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Editorial

NUCLEAR SEX AND THE SEX CHROMOSOMES

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THE discovery of a sex difference in the mammalian resting nucleus was made in 1949 by Barr and Bertram.[1] This important observation, like so many others in the history of medicine, was due to a combination of chance and the meticulous recording of experimental data. Barr and Bertram were engaged in some neurophysiologic experiments, specifically on the effects of electrical stimulation of the hypoglossal nerve of the cat. While examining the altered neurones histologically they noted a distinctive mass of nuclear chromatin which varied in position from the nucleolus to the nuclear membrane. This "nucleolar satellite" could be seen only in some cats and was conspicuously absent in others. Various explanations of this inconsistency had to be excluded before it was realized that the nucleolar satellite was present in female cats but not in males.[2] The importance of this remarkable finding (which incidentally had eluded microscopists for over 70 years) was immediately recognized by Barr and his colleagues who extended their initial observation to other mammals including man.[3] The nucleolar satellite was renamed the sex chromatin.

Female cell nuclei in all human tissues contain the sex chromatin body, which, by routine histologic methods, is found to be a planoconvex mass about 1 micron in diameter, characteristically lying in close contact with the nuclear membrane. It is composed largely of desoxyribonucleic acid (DNA) and so is stained by the Feulgen procedure and the usual nuclear dyes. Male nuclei seldom show chromatin material large enough to be mistaken for the typical sex chromatin.

TABLE I. NUCLEAR SEX IN THE DIAGNOSIS OF SEX ANOMALIES

		NUCLEAR SEX	CHROMOSOME CONSTITUTION	GONADS	SEX DIFFERENTIATION		
					EXTERNAL GENITALS	GENITAL DUCTS	SECONDARY SEX DEVELOPMENT
True hermaphroditism	(a) Chromatin positive	+	46(XX)[34,35,36]	Testis or ovotestis and ovary or ovotestis	Ambiguous	♂ and ♀	M or F
	(b) Chromatin negative	−	?46(XY)		Ambiguous	♂ and ♀	M or F
Male pseudohermaphrodism	(a) Testicular feminization	−	46(XY)[37]	Testis	♀ May be clitoral enlargement	Usually only ♂	F
	(b) With ambiguous differentiation	−	46(XY)[38]	Testis	Ambiguous	♂ or ♀	M or F
Female pseudohermaphroditism	(a) Congenital adrenal hyperplasia	+	46(XX)	Ovary	♂	♀	M
	(b) Maternal androgens, etc.	+	?46(XX)	Ovary	♂	♀	F
Gonadal aplasia (Turner's syndrome, etc.)	(a) Chromatin negative	−	45(XO)[25]	Gonadal streak	♀	♀	—
	(b) Chromatin positive	+	46(XX)/45(XO)[33]	Gonadal streak	♀	♀	—
Primary microorchidism (Klinefelter's syndrome)	(a) Chromatin positive	+	47(XXY)[26]	Testis	♂	♂	M
	(b) Chromatin negative	−	46(XY)	Testis	♂	♂	M
Primary amentia and microorchidism with triple-X/Y		Double positive	48(XXXY)[32]	Testis	♂	♂	M
Ovarian dysgenesis with triple-X		Double positive	47(XXX)[31]	Ovary	♀	♀	F

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The technique of determination of nuclear sex is thus capable of distinguishing human tissue of male origin from tissue of female origin. It has been shown by many investigators that the correct sex of normal individuals can be diagnosed microscopically from skin biopsy specimens,[3] mucosal scrapings,[4] and from blood films[5] with complete reliability. In the diagnosis of sex anomalies and in other clinical applications, the most convenient method of nuclear sex determination is provided by the oral mucosal smear technique[4]; 30 to 60 per cent of suitable nuclei in female smears are found to contain the sex chromatin, which is invariably absent in male smears. It is customary to refer to a diagnosis of female nuclear sex as chromatin positive, and to a diagnosis of male nuclear sex as chromatin negative. Strict use of this nomenclature is important in the management of cases of human sex anomalies.

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NUCLEAR SEX IN CLINICAL MEDICINE

Nuclear sex determination has many useful applications, but by far the most important of these is in human intersexuality, where it stands as the most useful single diagnostic procedure. Other applications to problems of medical interest have been in the diagnosis of sex before birth,[6] calculation of the sex ratio of aborted fetuses,[7] study of the fate of homografts,[8] study of the pathogenesis of teratomas,[9] and the elucidation of the fetal and maternal components of the placenta.[10] The more important clinical conditions in which nuclear sex determination plays an important diagnostic role are listed in Table I with the appropriate sex chromatin findings, the sex chromosome constitution where this is known, and the type of sex differentiation.

The diagnostic importance of nuclear sex in these disorders is self-evident. In the specific example of female pseudohermaphroditism due to congenital adrenal hyperplasia, establishment of the correct diagnosis leading to early treatment with cortisone and desoxycorticosterone may even be lifesaving in some cases.

The most marked discrepancy between somatic appearance and nuclear sex is found in a proportion of patients with the Klinefelter and Turner syndromes. Here the sex anomaly appears as hypogonadism and not intersexuality, for there is rarely any ambiguity of the external genitals. Patients with Klinefelter's syndrome are males who show primary testicular atrophy sometimes associated with eunuchoidism and gynecomastia. Turner's syndrome, or more correctly gonadal aplasia, is found in women and is characterized by shortness of stature, failure to mature sexually at puberty, rudimentary ovaries, and often multiple congenital anomalies. These two conditions are not uncommon. Chromatin-positive Klinefelter's syndrome has been estimated to occur approximately once in every 400 male births,[11] to account for about 3 per cent of male subfertility,[12] and to occur in 1 to 2 per cent of all mentally defective males.[13-15] Nuclear sex determination is thus indicated as a routine procedure in the investigation of severe male subfertility, and male hypogonadism. There is also much to be said in favor of making this simple test in the evaluation of mentally retarded males.

No exact evidence is as yet available on the frequency of chromatin-negative gonadal aplasia but it is clearly not as high as that of chromatin-positive Klinefelter's syndrome. Nuclear sex determination should be included in the investigation of young girls with retarded growth, of female children with bilateral inguinal hernias (to detect male pseudohermaphroditism), and in all cases of primary amenorrhea.

THE ORIGIN OF THE SEX CHROMATIN BODY

There has been much speculation about the origin and significance of the sex chromatin body. The observation that the sex chromatin body in normal females sometimes appeared to be a double structure, together with the circumstantial evidence that it occurred only in individuals who carried two X-chromosomes, lent support to the hypothesis that it represents the heterochromatic portions of the two X-chromosomes visiable in the resting nucleus due to somatic pairing of the heterochromatic areas.[16] In the male the equivalent portion of the single X-chromosome was either insufficiently heterochromatic to be distinguished from the other nuclear chromocenters, or did not stain heterochromatically.

One of the obvious steps toward solving the problem of the origin of the sex chromatin body was to relate the nuclear sex finding to the sex chromosome consitution. This was particularly important where the nuclear sex diagnosis was at variance with the somatic appearance as in chromatin-positive Klinefelter's syndrome and chromatin-negative Turner's syndrome. Technical difficulties at first prevented this, and led to a search for other types of evidence. A most valuable contribution came from the study of the incidence of color-blindness in the sex anomalies. Red-green color blindness is inherited as a sex-linked recessive character, the mutant genes responsible for the defect being carried on the non-homologous portion of the X-chromosome. Consequently, the frequency of color vision defect is much higher among males (approximately 7 per cent), who have only one X-chromosome, than among females (approximately 0.6 per cent), who have to be homozygous for the mutant gene to manifest the defect. In chromatin-negative gonadal aplasia the frequency of color vision defect corresponds to that expected in a male population,[17] and this suggests that these individuals have only one X-chromosome. In chromatin-positive Klinefelter's syndrome the evidence at first pointed to a frequency comparable to that in a normal female population,[18] but recent data raise the incidence to a level between the normal figures for males and females, indicating a more complex situation[19].

In 1959 identification of the sex chromosome complement in these sex anomalies was finally achieved. Progressive improvement in cytologic technique during the previous few years had led to a reasonably accurate analysis of the human chromosome constitution.[20-24] The basic chromosome number was firmly established as 46:44 autosomes and 2 sex chromosomes, paired in the female (XX) and unpaired in the male (XY). Klinefelter's and Turner's syndromes were among the first congenital disorders to be submitted to chromosome analysis and an obvious abnormality was found in each. Persons with chromatin-negative

gonadal aplasia were found to have 45 chromosomes of which only one was an X-chromosome,[25] whereas those with chromatin-positive Klinefelter's syndrome had 47 chromosomes, the additional one being a sex chromosome giving a complement of two X's and one Y.[26] These findings appeared to substantiate the reliability of the sex chromatin as a satisfactory marker of the presence of two X-chromosomes.

Observations on nuclear sex dimorphism and sex determination in some lower species are, however, not in accord with the hypothesis that the sex chromatin represents parts of two X-chromosomes. For instance, the larvae of the silkworm[27] and the spruce budworm[28] show "sex chromatin" in the heterogametic sex (XY), which in the Lepidoptera is the female. In the chicken, the male (ZZ) is again the homogametic sex, and it is the female with only one sex chromosome (ZO or ZW) that shows a sex chromatin mass.[29] If the sex chromatin is directly associated with the sex chromosomes in the chicken it must be formed by one sex chromosome only.

Support for this alternative hypothesis is suggested by the recent studies of Ohno and associates[30] on the nuclei of regenerating liver in the rat. In this mammal a distinct chromocenter was found in the female interphase nucleus but was absent in the male nucleus. At the prophase stage of mitosis in the female, one chromosome was remarkable in that it showed positive heteropyknosis compared with the other chromosomes, and also had a characteristic U-shaped appearance. This chromosome was not identified in prophase nuclei in the male. The authors concluded that of the two X-chromosomes in the female, one showed positive heteropyknosis at prophase and this alone formed the sex chromatin body seen in the interphase nucleus. The apparent double nature of the sex chromatin body was explained by folding. It was further suggested that although the male never showed the heteropyknotic chromosome at prophase it was this chromosome which became heteropyknotic when transmitted to female offspring. (It is interesting to note that a similar heteropyknotic chromosome was observed independently by Tjio and Östergren[39] in mammary carcinomas in milk virus strains in the mouse, although a different interpretation of the findings was presented.)

If these findings in prophase nuclei are confirmed in man, a solution will be provided for two important observations. The first of these is the demonstration of two sex chromatin bodies in two recently discovered sex chromosome anomalies, the XXX "superfemale" described by Jacobs and co-workers,[31] and the XXXY individuals with primary amentia and microorchidism.[32] In both these disorders two sex chromatin bodies are apparently associated with three X-chromosomes. Two single heterochromatic X-chromosomes, each forming a sex chromatin body, would provide a more satisfactory explanation for the findings than would the earlier hypothesis requiring somatic pairing, and in these instances, *four* X-chromosomes.

The second observation concerns a chromatin-positive case of gonadal aplasia described by Grumbach[33] to have only 45 chromosomes and an XO sex chromosome constitution. If the sex chromatin is directly related to the sex chromosomes in this case, it must clearly be derived from a single X-chromosome.

If the hypothesis that the sex chromatin is derived from heterochromatic regions of a single X-chromosome is correct, then it would follow that the properties of the two X-chromosomes are different in female somatic nuclei. It would seem very unlikely that in man there are two types of X-chromosome which segregate independently at meiosis, for if this were the case presumably four types of individual would be produced (i.e., chromatin-positive and chromatin-negative females, and chromatin-positive and chromatin-negative males). One might explain the dissimilar behavior of the two X-chromosomes as a change induced by paternal transmission and lost during oogenesis. At the present time there is no direct evidence to suggest how such differentiation of the X-chromosomes could occur.

SEX DETERMINATION IN MAN

Until recent times, theories on sex determination in man have been based largely on studies in Drosophila where sex is determined by a balance between male determining genes carried on the autosomes and female determining genes carried on the X-chromosomes, the Y playing no significant part in this system. The finding of an XXY sex chromosome complement associated with male gonadal differentiation in chromatin-positive Klinefelter's syndrome and an XO sex constitution associated with female sex differentiation in chromatin-negative Turner's syndrome, suggests that the Y chromosome plays an important role in male determination in man. Table I shows that with the exception of chromatin-positive true hermaphroditism, male gonadal differentiation in all the sex anomalies is associated with the presence of a Y chromosome. No satisfactory explanation of this exception has been provided although it is possible that more refined techniques in the future will demonstrate evidence of a translocation involving the Y chromosome.[36] It is equally possible that partial male differentiation is not the result of an abnormal genotype and a disordered sex-determining system but rather of an environmental defect affecting the early embryo.

CONCLUSION

Ten years after the observation of sex dimorphism in mammalian nuclei, the sex chromatin continues to raise more theoretical problems than it solves, and there is increasing speculation as to its origin. Despite this, it has played a very practical and important part in the diagnosis and understanding of human intersexuality and, in uncovering the sex chromosome anomalies, has demonstrated a new etiological mechanism in human congenital disorders.

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HORMONE THERAPY OF THE ADULT NEPHROTIC SYNDROME OF UNKNOWN ETIOLOGY

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ADRENAL cortical hormones have been demonstrated to induce a complete remission in certain cases of the nephrotic syndrome.[1-9] The great majority of clinical investigations concerning this phenomenon have been performed on patients in the first decade of life. In this age group the most common cause of the nephrotic syndrome is a disease of unknown etiology but of reasonably well-documented natural history.[5] It has been possible, therefore, to evaluate the effects of such therapy in childhood.

Adults have the nephrotic syndrome less frequently than do children, and it may be the result of one of several different disease processes. Thus, diabetes mellitus, amyloidosis, lupus erythematosus, multiple myeloma, or renal vein thrombosis can result in the nephrotic syndrome, as can subacute, chronic, or membranous glomerulonephritis. Biopsy studies[10] reveal a variety of glomerular changes not all of which, to date, have been well correlated with specific clinical entities of known natural history. Therefore, among adults with the nephrotic syndrome it is difficult to isolate a truly homogeneous group of patients. Hence, the response to treatment is correspondingly more difficult to evaluate than in children. This report describes the results obtained from adrenal cortical or corticotropic hormone therapy of the nephrotic syndrome in adults in whom no etiological diagnosis could be established.

PLAN OF STUDY

Patients with the nephrotic syndrome were hospitalized when first seen. Table I lists the pertinent historical and laboratory data for each patient. Treatment was undertaken in those individuals in whom no known disease process

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A portion of this study was presented at the National Kidney Disease Foundation Proceedings of the Tenth Annual Conference on the Nephrotic Syndrome, New York, 1958, by R. S. Post.

TABLE I. PERTINENT MEDICAL HISTORY AND LABORATORY DATA OBTAINED FROM ALL PATIENTS BEFORE HORMONE THERAPY WAS BEGUN

PATIENT	AGE	RACE	SEX	PERTINENT HISTORY	EDEMA	PROTEINURIA (GM. PER 24 HR.)	URINE SEDIMENT		BLOOD PRESSURE	SERUM ALBUMIN (GM. PER 100 ML.[11,12])	SERUM CHOLESTEROL (MG. PER 100 ML.[13])	MISCELLANEOUS DATA
							CENTRIFUGED CELLS (H.P.F.)	ADDIS COUNT (CELLS PER 12 HR.)				
1	26	W	F	Onset of edema in February, 1950, during sixth month of pregnancy; normal delivery; progressive edema; admitted July 27, 1950.	++++	12	R.B.C. 0 W.B.C. 10 Granular casts		170/110	1.4	765	Hgb. 13.2 Gm. R.B.C. 4.8 million. Throat culture: normal flora. Urine culture: no growth. Urea clearance: 26% normal. Congo red: 49% retained in serum. Fasting blood sugar: 80 mg. %. ECG: normal. Chest x-ray: pleural effusion, left.
2	22	N	M	Normal urinalysis November, 1951, (draft physical examination); 4 wk. before admission: pharyngitis, cervical adenitis, malaise; edema appeared 5 days before admission; admitted May 26, 1952.	++	9		R.B.C. 22.5 million W.B.C. 17.5 million Granular casts	145/80	1.5	506	Hgb. 16.5 Gm. R.B.C. 6.0 million. Throat culture: normal flora. Urine culture: no growth. Urea clearance: 59% normal. Chest x-ray: pleural effusion, left. ECG: normal. Fasting blood sugar: 70 mg. %. (May 21, 1956, after upper respiratory infection and relapse: ASO < 100.)
3	28	W	F	Normal urinalysis Feb. 16, 1954, with last of 3 normal pregnancies; 2 mo. before admission: upper respiratory infection followed by weight gain and edema; admitted Nov. 27, 1954.	++	7	R.B.C. 0 W.B.C. occasional Granular casts		110/70	1.3	1,262	Hgb. 15.0 Gm. R.B.C. 5.5 million. Throat culture: normal flora (Oct. 24, 1959). ASO < 50 (Oct. 24, 1959). Urea clearance: 28% normal. Chest x-ray: bilateral pleural effusion. ECG: normal. Fasting blood sugar: 81 mg. %.
4	29	W	F	Three normal pregnancies, last 20 mo. before admission; rapid onset of edema October, 1953; admitted April 11, 1954.	++++	8		R.B.C. 3.1 million W.B.C. 24 million Granular casts	140/90	1.3	940	Hgb. 16.3 Gm. R.B.C. 5.3 million. Throat culture: normal flora. Urine culture: no growth. Urea clearance: 60% normal. L.E. prep: negative. Chest x-ray: normal. ECG: normal. Fasting blood sugar: 70 mg. %. (June 17, 1956, relapse; ASO < 125.)
5	45	N	F	Normal urinalysis 4 mo. before admission; upper respiratory infection without sore throat or fever 3 to 4 wk. before admission; edema 5 days before admission on Oct. 27, 1953.	+	12	R.B.C. 4-8 W.B.C. 5-10 Granular casts		150/80	1.9	360	Hgb. 12 Gm. R.B.C. 3.4 million. Throat culture: normal flora. Urine culture: Aerobacter aerogenes. Urea clearance: 9% of normal. Congo red: 50% retained in serum. Chest x-ray: left pleural effusion. Retrograde urogram: normal. Fasting blood sugar: 74 mg. %. L.E. prep: negative. ECG: low voltage.

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6	28	W	M	Six mo. before admission: routine physical examination for "nervous stomach" revealed proteinuria; armed forces 1943 to 1946; normal urinalyses; ankle edema appeared 3 mo. before admission on Nov. 22, 1957.	++	11	R.B.C. 13 million W.B.C. 10 million Granular casts	140/85	2.2	492	Hgb. 11 Gm. HCT. 35%. Urea clearance: 78% normal. L.E. prep: negative. Chest x-ray: normal. Gastrointestinal series: normal. Intravenous urogram: normal. ECG: normal. Fasting blood sugar: 98 mg. %.
7	29	N	F	Normal pregnancy and urinalysis in February, 1947; rapid onset and progression of edema 3 wk. before admission on July 26, 1954.	++++	3	R.B.C. occasional W.B.C. 1-3 Granular casts	120/70	0.7	742	Hgb. 14 Gm. HCT. 44%. Throat culture: normal flora. Urine culture: no growth. Urea clearance: 65% normal. L.E. prep.: negative. Chest x-ray: pleural effusion, left. ECG: low voltage. Fasting blood sugar: 81 mg. %.
8	69	N	F	Documented hypertension 1941; aortic stenosis and insufficiency; duration ?; 3 mo. before admission: "flu-like" illness without sore throat; onset of edema shortly thereafter; admission Feb. 17, 1958.	++	4	R.B.C. 5.0 million W.B.C. 31.6 million Granular casts	210/80	2.1	472	Hgb. 11.4 Gm. R.B.C. 4.5 million. Urine culture: no growth. ASO. < 166. Urea clearance: 33% normal. L.E. prep.: negative. Chest x-ray: cardiac enlargement, predominantly left ventricular. Retrograde urogram: normal. ECG: left ventricular hypertrophy. Fasting blood sugar: 80 mg. %.
9	55	N	M	Documented hypertension 1953; trace urine protein, minimal edema, serum albumin 4.0 Gm. per 100 ml. and mild cardiac failure was present; 1 mo. before admission edema progressed rapidly; admitted May 27, 1955.	++++	12	R.B.C. 20-25 W.B.C. 6-10 Granular casts	200/108	2.1	275	Hgb. 10.6 Gm. HCT. 33%. Throat culture: normal flora. Urine culture: no growth. Urea clearance: 36% normal. Femoral venous pressure 130 mm. saline when antecubital 110 mm. saline. Chest x-ray: cardiac enlargement, pleural effusion. Cystoscopy and retrograde urograms: normal. ECG: left ventricular hypertrophy. L.E. prep.: negative.
10	66	N	M	Onset of edema and proteinuria 1 yr. before admission; progression of edema 3 mo. before admission; admitted Feb. 1, 1951.	++	8	R.B.C. 0 W.B.C. 80-90 Granular casts	170/85	2.4	618	Hgb. 14.9 Gm. R.B.C. 5.0 million. Urine culture: Aerobacter aerogenes. Urea clearance: 68% normal. Cystoscopy and retrograde urograms revealed duplication of right upper urinary tract, "low-grade" cystitis, and benign prostatic enlargement. Congo red: 50% retained in serum. Chest x-ray: minimal bilateral pleural effusion. ECG: slight prolongation of P-R interval. Fasting blood sugar: 86 mg. %.

TABLE I. PERTINENT MEDICAL HISTORY AND LABORATORY DATA OBTAINED FROM ALL PATIENTS BEFORE HORMONE THERAPY WAS BEGUN—(CONT'D)

PATIENT	AGE	RACE	SEX	PERTINENT HISTORY	EDEMA	PROTEINURIA (GM. PER 24 HR.)	URINE SEDIMENT		BLOOD PRESSURE	SERUM ALBUMIN (GM. PER 100 ML.[11,12])	SERUM CHOLESTEROL (MG. PER 100 ML.[13])	MISCELLANEOUS DATA
							CENTRIFUGED CELLS (H.P.F.)	ADDIS COUNT (CELLS PER 12 HR.)				
11	48	W	M	Insurance physical examination: normal August, 1956; upper respiratory infection without sore throat or fever in October, 1956, followed by progressive edema; August, 1957, pulmonary infarction occurred; admitted Nov. 10, 1957.	++	7		R.B.C. 6.7 million W.B.C. 12.6 million Granular casts	130/80	2.1	500	Hgb. 14.2 Gm. HCT. 47%. Urea clearance: 85% normal. Chest x-ray: consistent with residua of pulmonary infarction. Intravenous urogram: kidney size upper limits of normal. ECG: incomplete bundle branch block. L.E. prep.: negative. Fasting blood sugar: 79 mg. %.
12	22	W	F	At age 9 had proteinuria and edema diagnosed as chronic glomerulonephritis; occasional recurrent edema since and persistent proteinuria; age 20: pregnancy interrupted at 5 wk. because of hypertension; admitted March 1, 1955.	0	5		R.B.C. 74 million W.B.C. 7 million Granular casts	160/70	2.3	525	Hgb. 12.2 Gm. R.B.C. 4.0 million. Urea clearance: 32% normal. Chest x-ray: normal. Intravenous urogram: normal. ECG: normal.
13	36	W	M	Normal urinalysis Dec. 4, 1943; insidious onset and progression of edema, May, 1954; admitted March 24, 1955.	++	13	R.B.C. 50-60 W.B.C. 15-20 Granular casts		160/90	2.9	380	Hgb. 9 Gm. R.B.C. 3.3 million. Throat culture: normal flora. Urine culture: no growth. Urea clearance: 37% normal. Tongue biopsy: normal. Chest x-ray: cardiac enlargement. Intravenous urogram: normal. ECG: auricular P.B. and early left ventricular hypertrophy. Fasting blood sugar: 114 mg. %.

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could be established as the cause for the nephrotic syndrome. For purposes of evaluation, the treatment program was divided into short-term therapy and maintenance therapy.

Early in this study, short-term therapy consisted of intravenous ACTH (20 to 40 mg.) administered each day over an 8-hour period for a total of 10 to 14 days. If the patient responded to this treatment and then relapsed, the treatment course was repeated. If no response occurred, the treatment was repeated when possible with the same or a larger dose of drug after a period of rest. Recently, prednisone* (40 to 80 mg. orally per day) has been used in place of ACTH. We have not attempted to compare the relative effectiveness of a number of different therapeutic regimens in each patient. Instead, we have attempted in each case to treat with the minimum dose of drug required to induce a remission. In unresponsive patients we have attempted to use the maximum dose tolerated by the patient.

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Maintenance therapy when first used in this study consisted of intramuscular depot ACTH.† Eighty clinical units of this material was administered on 3 consecutive days of each week. This treatment schedule was used when a short course of therapy induced a partial or complete remission but a relapse occurred some time after the completion of the short course of treatment. More recently, prednisone has been substituted for the intramuscular ACTH in the maintenance treatment schedule. The rapidity with which the dose of prednisone or other maintenance drug was reduced has been determined by the presence or absence of untoward responses to the drug and the status of the proteinuria. If proteinuria returned or increased as the maintenance drug was decreased in dose, the dose of drug was promptly returned to or toward the initial dosage level. When a remission was again established, the dose of drug was once more diminished slowly and an attempt made to finally discontinue hormone therapy.

A prolonged schedule of treatment was instituted for 2 patients who did not respond to a short course of treatment. This was done to determine whether a slow response to treatment might be observed over a long period of time in the absence of a response to short-term therapy.

All patients were placed on restricted sodium intake. The degree of sodium restriction was dictated by the amount of edema present, the degree of hypertension, and the degree of renal failure. If there was a tendency for the patient to gain weight and become hypertensive with treatment, a 200-mg. sodium diet was prescribed. Supplementary potassium was used with initial therapy or with the higher doses of maintenance drugs, with special caution in the presence of hyponatremia, during dietary sodium restriction,[14] or when severe renal failure was present. Blood pressure and weight changes were carefully observed during treatment. Oral antacid preparations have been used routinely, but a strict ulcer regimen was not prescribed. Roentgenologic examinations of the chest, gastrointestinal tract, and bones were performed initially and at intervals as indicated.

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*Supplied in generous quantities as Meticorten by Schering Corporation, Bloomfield, N.J.

†ACTX, a depot form of ACTH in 4 per cent phosphorylated hesperidin, generously supplied by The National Drug Company, Philadelphia, Pa.

The results of hormone therapy were evaluated by measurements of 24-hour urine protein excretion, weight loss or gain, and the concentration of albumin and cholesterol in the serum and by changes in the urea clearance. The most re-

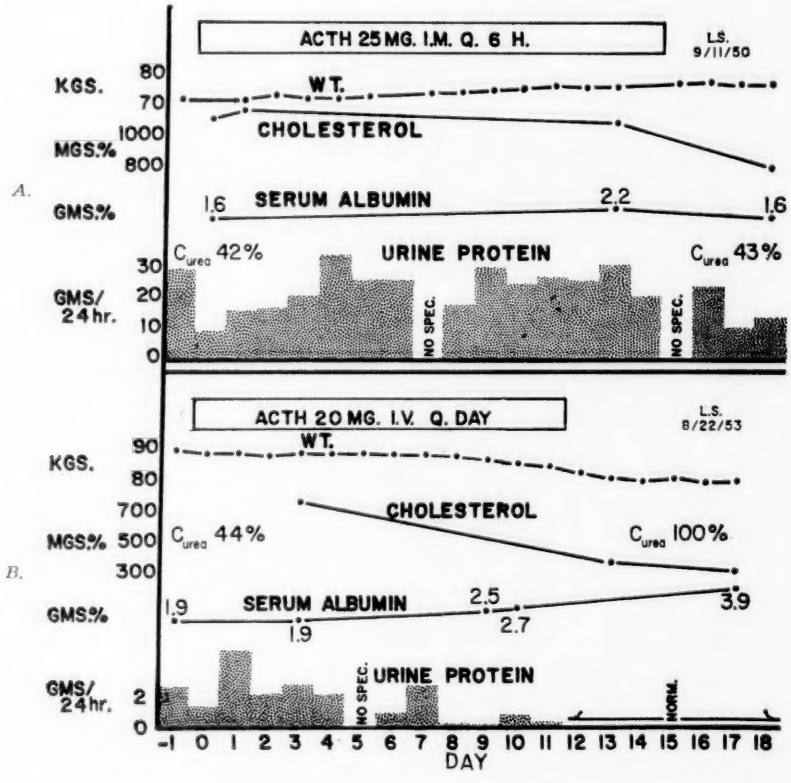

Fig. 1.—Short-term treatment in patient 1. *A*, No response to intramuscular ACTH (25 mg.) every 6 hours for 14 days. *B*, Complete response to intravenous ACTH (20 mg.) every day for 11 days.

liable indication of a response to treatment has been a decrease in the total amount of protein excreted in the urine per 24 hours. Twenty-four–hour urine collections were obtained daily whenever possible and the protein content determined by the Shevky and Stafford[15] technique.* When ambulatory patients

*The minimum volume of precipitate which can be measured accurately with the calibrated tubes used for this determination is 0.01 ml. This is equivalent to 0.072 mg. of protein per milliliter of urine or 144 mg. per day if the urine volume is 2,000 ml. Since the urine volume rarely exceeds 2 L. after a diuresis has occurred and proteinuria has returned to normal, 144 mg. of protein per day represents the maximum amount of proteinuria which can escape accurate measurement. Patients excreting less than this amount cannot be distinguished from normal persons unless an attempt is made to concentrate the urine routinely. Since this has not been done we have designated as "normal" or "negative" all quantitative protein values below 144 mg. per 24 hours.

were in relapse, they were instructed to bring in aliquots of daily 24-hour urine specimens. Whenever possible, the urine of patients in remission was analyzed weekly for protein content. Out of town patients were supplied with protein

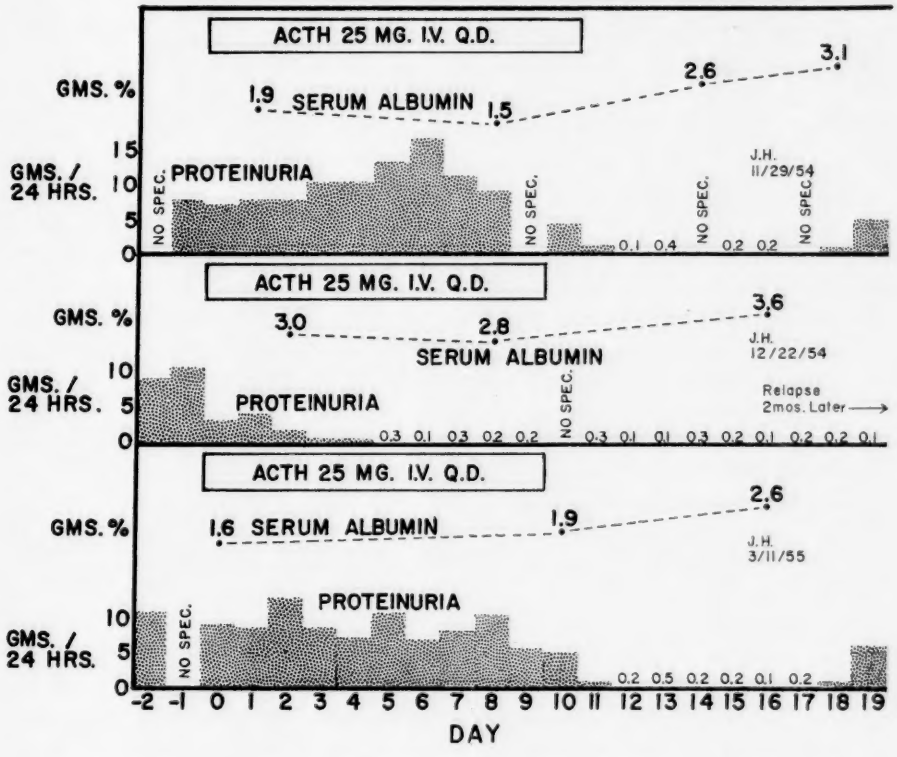

Fig. 2.—Relapses in patient 3 following completion of three short-term treatment courses.

test papers* so that daily tests of urine protein excretion might be carried out and so that an increase in urine protein heralding a relapse in the disease could be detected at the earliest possible moment.

RESULTS

In the Appendix are listed the pertinent observations before and after treatment for all patients in the study and an indication of whether each patient responded to short-term intensive or maintenance therapy or both with a decrease in proteinuria. In no instance was a significant improvement observed in any of the parameters studied without a concomitant improvement in proteinuria. Thirteen patients were studied: 3 Negro females, 4 white females, 3

*Generously supplied by Eli Lilly & Company, Indianapolis, Ind.

Negro males, and 3 white males. Five patients exhibited a response to short-term treatment (patients 1 through 5, Table I). All of these 5 patients have responded to maintenance therapy and have remained in remission as long as such therapy has been continued. Two others (patients 6 and 7, Table I) have apparently responded to therapy of long duration despite the fact that no response was observed to short-term therapy. Six (patients 8 through 13, Table I) did not improve with short-term therapy and were not placed on a maintenance regimen.

RESPONSIVE CASES

Short-term Treatment.—Short-term hormone therapy in patients 1 through 5 was accompanied by (1) a diuresis if edema was present, (2) a return of the altered serum concentrations of albumin and cholesterol to or toward normal, and (3) a disappearance of proteinuria (patients 1, 3, and 4) or a significant decrease in proteinuria (patients 2 and 5). The urea clearance increased if it was low at the start of treatment. In each instance in which proteinuria recurred following a successful short-term treatment course, repetition of the short-term course again induced as complete a remission. Fig. 1 compares a successful (*B*) and an unsuccessful (*A*) course of ACTH in patient 1 and shows the complete and dramatic improvement that may accompany short-term hormone therapy in a responsive patient. As shown in Fig. 1, the proteinuria was considerably less at the time patient 1 responded to treatment, but all other aspects of the nephrotic syndrome were comparable and we have no reason to believe that this lower protein excretion in any way determined her response at that time.

Patients 2 through 5 relapsed after short-term therapy in the absence of subsequent maintenance therapy. Patient 1 received maintenance therapy after her first response to treatment, and a relapse was not observed. In patients 2 through 5 the increase in proteinuria occurred an average of 14 days (extremes, 4 and 67 days) after the cessation of short-term treatment. Fig. 2 illustrates the rapid return of proteinuria observed in patient 3 following the cessation of her short-term therapy. The remission obtained from a short course of therapy did not continue unless maintenance therapy was given. That this latter was required to maintain a remission is shown in Fig. 3.

Maintenance Therapy.—It has been necessary to continue maintenance therapy until the present time in 3 patients (2, 3, and 5, Table I) because an increase in or a return of proteinuria has occurred each time the maintenance drug was diminished in dose or stopped. Maintenance therapy was discontinued after 2 years with patients 1 and 4, and they have remained well for 3½ years and 8 months, respectively.

Patient 1 was treated with cortisone (200 mg. per day) after her response to intravenous ACTH (see Fig. 1,*B*). This dose was decreased gradually and the drug discontinued in January of 1956, 2 years and 3 months after it was begun. In 1956 a normal pregnancy was completed. She has not been available for our personal evaluation since 1955, but a routine urinalysis was reported by her physician as normal and no signs or symptoms of the nephrotic syndrome were present in March of 1959.

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Patient 4 is the only other one in remission without maintenance therapy at the present time. This patient relapsed 2 months after a 1½-year course of depot ACTH was completed. Prednisone then induced a remission and was continued. This drug was gradually withdrawn over a 2-year period and then stopped. Eight months later she was still in complete remission.

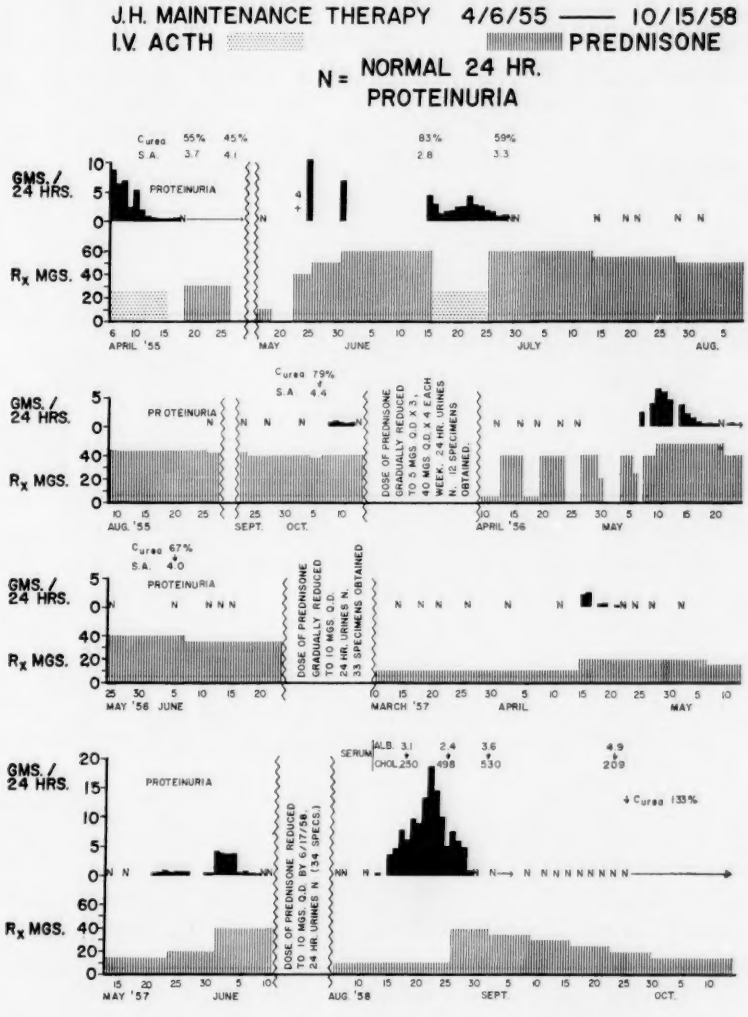

Fig. 3.—Response to prolonged therapy in patient 3.

The remaining 3 patients in the responsive category (2, 3, and 5, Table I) have required continuous treatment to maintain an optimum remission. They have demonstrated an unequivocal response to an increase in the dose of drug

used for maintenance therapy on each occasion when significant proteinuria has developed in the course of a decreasing dosage schedule. Patient 2 is the only one of the group who has not progressed to the point of normal proteinuria on maintenance therapy. This patient was lost to the study with less than 1 year of maintenance therapy.

Fig. 3 shows the maintenance therapy of patient 3 in detail. It compares proteinuria and the dose of drug administered for maintenance therapy and illustrates the sensitivity to drug dosage that this patient has demonstrated throughout her course. After maintenance therapy was begun, proteinuria returned on six occasions. Only the last of these was accompanied by weight gain and edema. With each relapse the dose of prednisone was increased to 40 mg. per day and was accompanied by a disappearance of proteinuria in from 5 days to 1 month. Three and one-half years after maintenance therapy was begun (August, 1958) proteinuria returned, but the dose of prednisone was continued at 10 mg. per day. Daily 24-hour urine collections were obtained, and the concentrations of albumin and cholesterol in the serum were determined frequently. Twelve days after the onset of abnormal proteinuria the patient observed puffiness of her eyes and noticed that her clothes were tight. A 5-pound weight gain occurred and edema with one to two plus pitting was present in the lower extremities. The dramatic change in serum albumin and cholesterol is shown in Fig. 3. Prednisone (40 mg. per day) was given and the proteinuria returned to normal 5 days after the dose was increased. The concentrations of albumin and cholesterol in the serum were normal 1 month later. Fig. 3 shows that proteinuria had decreased from a peak of 18 Gm. per day to 5 to 7 Gm. per day at the time clinical signs became manifest and the dose of prednisone was increased. It is possible that this decrease in proteinuria marked the beginning of a spontaneous remission. We have not observed a spontaneous remission in adults. The increasing edema and altered serum concentrations of albumin and cholesterol at the time the dose was increased led us to conclude that the ensuing events occurred in response to treatment.

The maintenance treatment course of patient 5 is shown in Fig. 4. We have interpreted the results of the short-term course beginning April 21, 1954, as indicating a significant though transitory decrease in proteinuria. (See the Appendix for previous short-term therapy.) Patient 5 illustrates two points worthy of emphasis. The first is the slow diminution in proteinuria observed during the first 2 years of maintenance therapy. It is possible that this was the result of inadequate therapy, but the results differ sharply from those obtained with patients 1 through 4 and are similar to those obtained with patients 6 and 7 discussed below. In these latter 2 patients it has appeared that the disease may require many months to respond to treatment.

The second point is that later relapses in patient 5 have responded more quickly to an increase in the dose of the maintenance drug than did the initial relapse. At the present time when a relapse occurs the administration of a dose of 40 mg. of prednisone per day is followed by the disappearance of proteinuria within less than a month. Our impression is that at present the disease process is more responsive to hormone therapy than it was at the beginning of her illness.

The disease in patient 5 thus appears to be transitional between those of patients 1 through 4 and patients 6 and 7. At the present time this patient is not free of proteinuria unless she receives 40 mg. of prednisone per day. The increases in proteinuria have not been accompanied by other manifestations of the nephrotic syndrome since the initial episode (see appendix).

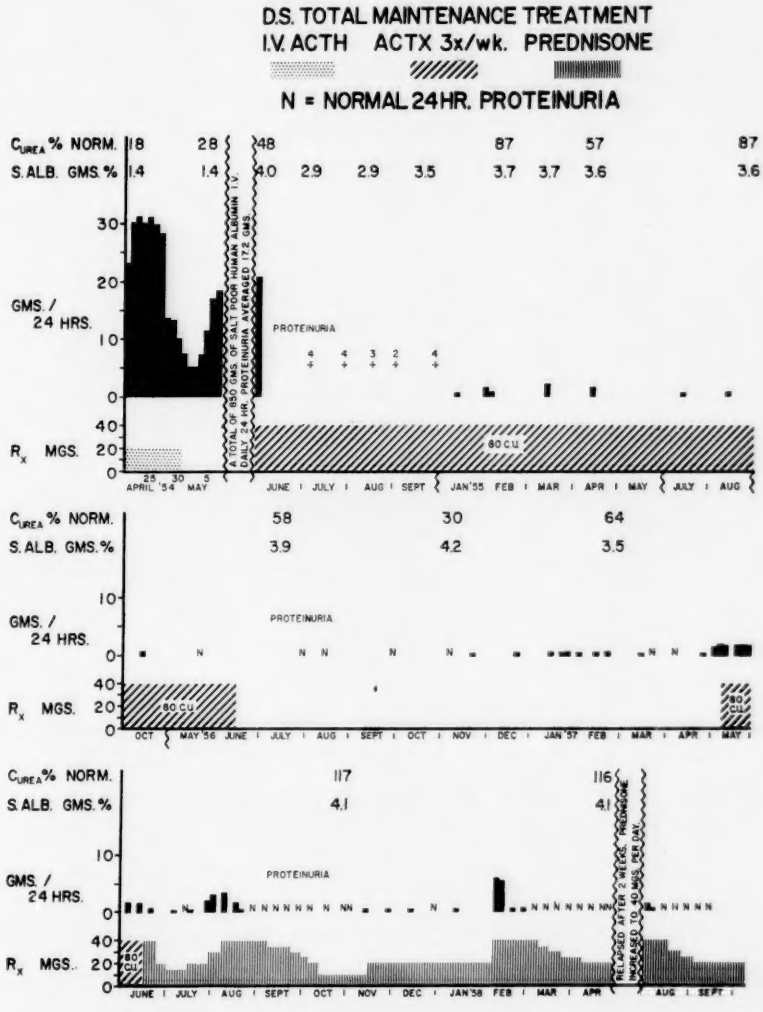
D.S. TOTAL MAINTENANCE TREATMENT
I.V. ACTH ACTX 3x/wk. PREDNISONE
N = NORMAL 24 HR. PROTEINURIA
C UREA % NORM.
S. ALB. GMS. %
GMS. / 24 HRS.
PROTEINURIA
A TOTAL OF 850 GMS OF SALT POOR HUMAN ALBUMIN I.V. DAILY X 4 DAYS. PROTEINURIA DECREASED 172 GMS.
Rx MGS.
80 CU
APRIL '54 MAY JUNE JULY AUG SEPT JAN '55 FEB MAR APR MAY JULY AUG
OCT MAY '56 JUNE JULY AUG SEPT OCT NOV DEC JAN '57 FEB MAR APR MAY
JUNE JULY AUG SEPT OCT NOV DEC JAN '58 FEB MAR APR AUG SEPT
RELAPSED AFTER 2 WEEKS PREDNISONE INCREASED TO 40 MGS. PER DAY

Fig. 4.—Response to prolonged therapy in patient 5.

Two patients (6 and 7) were selected from the group of 8 patients who exhibited no response to therapy of short duration and were treated for a period of time considerably longer than that used for short-term therapy. This was

done in an attempt to determine the duration of treatment required before a patient is to be considered unresponsive to hormone therapy. These 2 patients were selected because they tolerated the drugs used quite well and they were quite cooperative and hence could be expected to remain in close contact with the physician.

Fig. 5 shows the total treatment course of patient 6, who exhibited no significant change in proteinuria while receiving 40 mg. of prednisone per day for 12 days. This dose was increased to 80 mg. per day and continued for a period of 3 months. At this time it appeared possible that the proteinuria was diminishing. Consequently treatment was continued, but the dose of prednisone was gradually diminished and discontinued 10 months after it was started. The 24-hour proteinuria continued to diminish slowly and at the time treatment was stopped it was 1.5 to 2 Gm. compared to 10 Gm. at the onset of therapy. Improvement continued, but to date the proteinuria has not diminished below

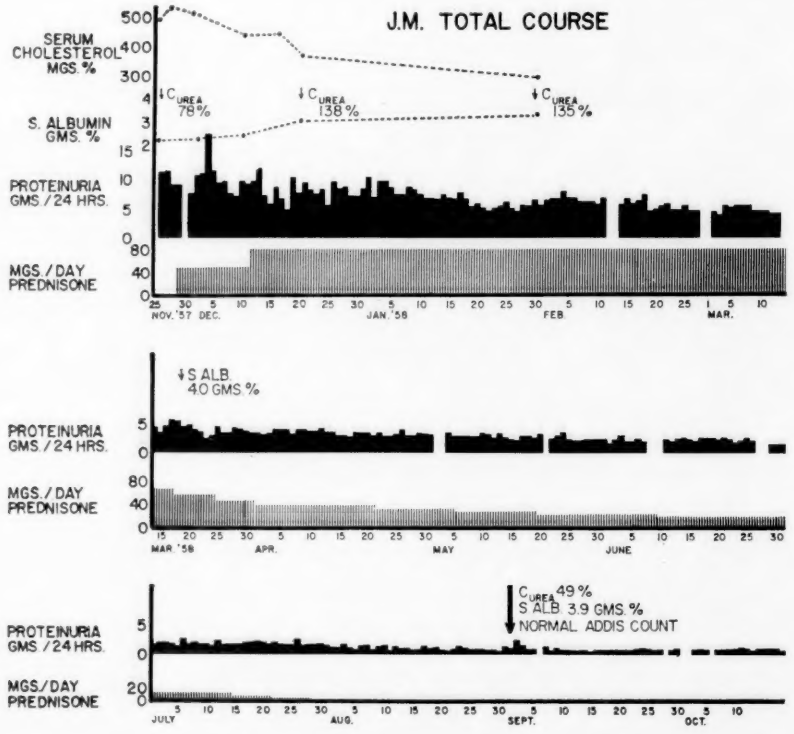

Fig. 5.—Response to prolonged therapy in patient 6. Urea clearance 99 per cent of normal in December of 1958.

1 Gm. per 24 hours. In December of 1958 the urea clearance was 99 per cent of normal and the concentrations of cholesterol and albumin in the serum were normal.

Patient 7 (see Fig. 6) did not respond to two courses of 25 mg. of ACTH intravenously or to 40 mg. of ACTH intravenously. Depot ACTH, in doses of 80 clinical units on 3 consecutive days per week, was prescribed in February of

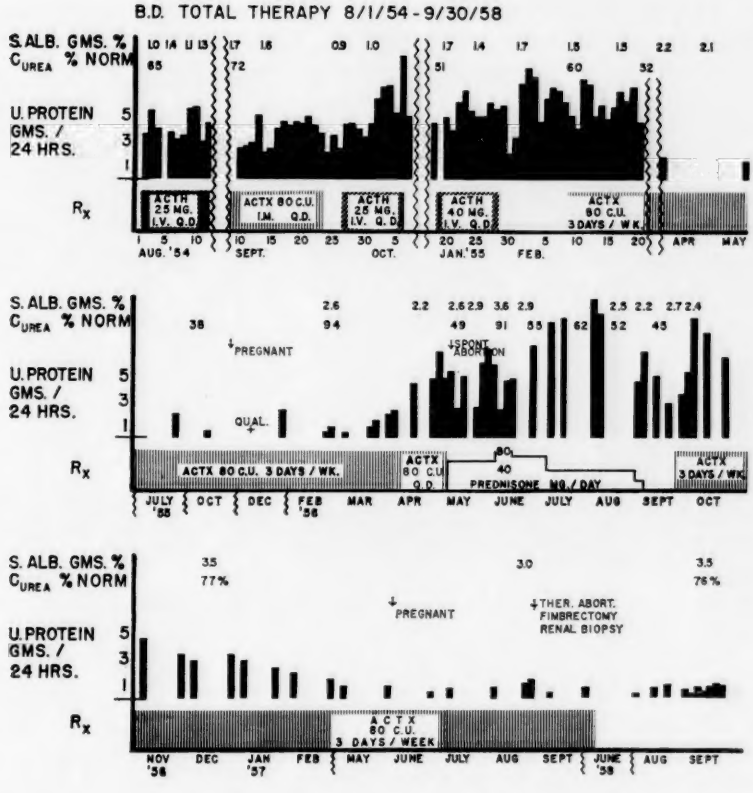

Fig. 6.—Total therapy, patient 7.

1955. The values for 24-hour urine protein excretion over the next year were all significantly lower than those values obtained during the initial treatment period. At the end of this period the serum albumin was 2.6 Gm. per 100 ml. as compared to an initial value of 1.0. A pregnancy supervened in December, 1955, and proteinuria gradually increased to over 10 Gm. per 24 hours despite continued therapy with depot ACTH, 80 clinical units per day. The patient spontaneously delivered a dead fetus of approximately 24 weeks' gestation (May, 1956). Therapy was continued with prednisone and then, once again, depot ACTH. A gradual diminution in proteinuria was observed over the next year as the maintenance regimen was continued. Once again a pregnancy occurred but was therapeutically interrupted before more than a slight increase in proteinuria had occurred.

A surgical renal biopsy specimen was obtained at this time and revealed marked, diffuse glomerular changes (see Fig. 7). Maintenance therapy was continued for a year and no decrease in proteinuria below the lowest observed value of 300 mg. per 24 hours was recorded. Therapy was then discontinued (June, 1958). On Sept. 3, 1958, the concentration of albumin in the serum was 3.5 Gm. per 100 ml., the concentration of cholesterol in the serum was 171 mg. per 100 ml., and the urea clearance was 76 per cent of normal.

The course of events observed in association with prolonged hormone therapy in patients 6 and 7 may not be a direct result of treatment. The natural history of this disease (or these diseases) in adults is not well enough documented to arrive at a definite conclusion. To relate the diminution in proteinuria, the improvement in the albumin and cholesterol concentrations, and the maintained or improved renal function to hormone therapy, one would have to observe a relapse in proteinuria without treatment and then demonstrate that a remission could be induced by hormone therapy. These 2 patients are being closely observed, but at present this has not occurred.

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UNRESPONSIVE PATIENTS

Six of 13 patients treated with one or more short-term courses of hormone therapy failed to exhibit a response and received no further hormone therapy (patients 8 through 13, Table I). In none of these 6 patients was a significant improvement in any of the parameters evaluated observed with hormone therapy, although some of the patients were benefited clinically by various diuretic regimens and by salt restriction.

Of the 6 patients who did not improve with short-term treatment, 4 died (patients 8, 10, 12, and 13), 1½, 5, 15, and 2½ years, respectively, after the onset of the edema. At the time of death (see Appendix) most of the characteristics of the nephrotic syndrome were gone. Patients 10 and 12 both died of uremia. Patient 13 died suddenly at home after experiencing symptoms of coronary artery insufficiency. Patient 8 had rheumatic heart disease with aortic stenosis and insufficiency and arteriosclerotic heart disease. Congestive heart failure was also present. She died at home of a myocardial infarction with ventricular rupture.

The remaining 2 patients are alive 3 years (patient 11) and 4 years (patient 9) after the onset of edema, without consistent changes in their clinical condition and with edema and persistent proteinuria.

COMPLICATIONS OF HORMONE THERAPY

No instance of gastrointestinal bleeding was observed. In no instance has infection occurred which was not apparent from clinical observation. Patient 3 developed a viral pneumonia at a time when the maintenance dose of prednisone was 40 mg. per day. No increase in proteinuria was observed and the course of the pneumonia was not unusual. Tetracycline was administered. Patient 4 developed acute purulent sinusitis with pain and fever at a time when the maintenance dose of prednisone was 240 mg. per week on an intermittent dosage

schedule. The sinusitis responded readily to penicillin therapy. Elevation of the total white blood cell count was routinely observed in patients receiving ACTH therapy and the larger doses of prednisone.

With patients 4 and 5, obesity has been a problem. A voracious appetite was induced by hormone therapy. Patient 4 gained 42 and patient 5 gained 45 pounds. Patient 4 was not disturbed by her appearance and could afford a new wardrobe. However, patient 5 was deeply disturbed by her appearance and could not afford the new clothes her altered dimensions required.

Characteristics of Cushing's syndrome have developed in all patients who have received short-term and maintenance courses of therapy with the larger doses of all drugs employed. All changes have readily reversed themselves as the dose of drug has been decreased or stopped.

Psychiatric complications were encountered rarely. Patient 5, who has underlying psychoneurotic difficulties of moderate severity, became quite agitated whenever the maintenance dose of prednisone was 40 mg. per day. Below this dose, however, there was considerable fluctuation in her emotional status and a direct relationship between the dose of prednisone and severe agitation could not be established. Patient 7 became quite euphoric and slightly confused on a dose of 80 mg. of prednisone per day after 2 weeks of therapy. All patients described some degree of euphoria and increased appetite with therapy. The intermittent dosage schedule of prednisone was in general unsatisfactory to the patient receiving it because of the swings in mood encountered as the drug was stopped and started. The intermittent depot ACTH did not seem to have this effect.

Hypertension was the reason for diminishing the dose of hormone in patient 7, who exhibited an elevation of blood pressure from 130/55 to 170/110 after the administration of prednisone in a dose of 80 mg. per day for 17 days. The dose was decreased to 40 mg. per day and 1 week later the blood pressure was 145/100. Facial and body characteristics of Cushing's syndrome, hirsutism, acne, slight mental confusion, and euphoria were associated with the increase in blood pressure and began to subside as the dose of prednisone was decreased.

Two patients showed a positive water balance with hyponatremia and hyperkalemia while receiving 50 mg. and 60 mg. of prednisone per day (patients 8 and 9) for 10 and 15 days, respectively. Both were receiving a 200-mg. sodium diet. Leutscher[16] has described this complication of steriod therapy. Laragh[14] has emphasized the susceptibility of the hyponatremic patient to potassium intoxication.

PATHOLOGY

The kidney tissue available for histologic examination was obtained from one surgical biopsy and three autopsies.

Fig. 7 is illustrative of the pathologic material available for study and was obtained from patient 7. Practically all glomeruli show thickening of the basement membrane. This was associated with narrowing of the capillary lumena, swelling of endothelial and epithelial cells, adhesions between adjacent tufts

and between tufts and the parietal layer of Bowman's capsule, and focal hyalinization. Some glomeruli were completely hyalinized. Tubular atrophy and a small number of colloid casts were present, as well as interstitial fibrosis and infiltration of lymphocytes. A few of the arterioles showed slight hyaline thickening of the intima.

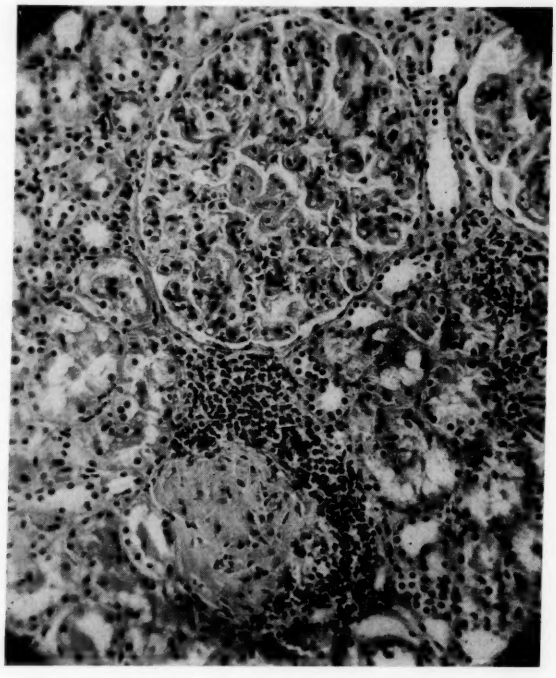

Fig. 7.—Surgical biopsy from patient 7. See text for description.

Autopsy material from patients 8, 10, and 12 exhibited the same glomerular changes as the biopsy from patient 7. Patient 12 revealed the most marked hyalinization of glomeruli. Patient 8 exhibited, in addition to the glomerular changes, a significant degree of arterial and arteriolar sclerosis of the renal blood vessels with areas of fibrinoid necrosis.

DISCUSSION

The beneficial effect of short courses of treatment with corticotropin (ACTH) or adrenal cortical steroid compounds in childhood nephrosis has been well documented in the literature.[1-9] Seventy per cent or more of children with this disease can be expected to respond to therapy with a prompt diuresis, a decrease or disappearance of abnormal proteinuria, and a return of altered blood chemical values to or toward normal.

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Certain adults will respond to hormone therapy in the same manner, but it is difficult to predict what proportion will so respond. Few adult cases have been reported and patients in the different studies have not been treated in the same manner. Goodman and Baxter[8] found that 5 out of 9 adults with a clearly defined nephrotic syndrome of unknown etiology responded well to short-term therapy. Three other patients in this group of 9 showed some response, but the duration of their treatment was longer than that used in our series for short-term therapy. Lange and colleagues[6] induced a diuresis in 13 of 19 adult patients with nephrosis and stated that, in all of these patients but 1, diuresis could be elicited with repeated trials of therapy. It is not clear what degree of improvement was observed in the other parameters of the disease coincident with the loss of edema. Danowski, Mateer, and Puntereri[9] found 15 per cent of an unselected group of adolescents and adults with proteinuria to be responsive to short-term steroid therapy. Five out of 13 patients in our study who received one or more short courses of hormone therapy responded unequivocally to this therapy. On the basis of the above experience and that presented in this paper, one may expect less than 50 per cent of a group of adult patients with the nephrotic syndrome of unknown causation to exhibit a decrease in proteinuria in response to hormone therapy. It is impossible to predict what the response to short-term treatment in a given adult with the nephrotic syndrome will be.

The high rate of relapse following short-term therapy was emphasized by Lange[17] in 1951, and he suggested that maintenance therapy should be used to prevent a relapse. The great majority of studies in children support this finding. Our data are in agreement and suggest that a high percentage of adults may be expected to relapse after they have responded to a short course of treatment.

The pediatric experience demonstrates that maintenance therapy will prevent a relapse from occurring during treatment if an adequate dosage schedule is used. Lange and co-workers[6] describe 5 adult patients treated for a minimum of 1 year who did not relapse during treatment. The 5 patients in our study who were demonstrated to be responsive to short-term therapy maintained a normal (4 patients) or near normal (1 patient) state as long as adequate maintenance therapy was administered. No patient relapsed while receiving such therapy unless the dose of the particular drug used to induce a remission was reduced too rapidly or discontinued.

The relapse rate to be expected in adult patients after a course of maintenance therapy has been completed is not known. Lange and co-workers[6] describe no relapses in 5 adult patients treated for 1 year and then observed for a minimum of 1 year. Two of our patients (3 and 4) have relapsed after 1 year of continuous maintenance therapy was discontinued. Patient 3 has had three relapses, each preceded by 1 year of maintenance therapy. Patient 5 relapsed after the completion of 2 years of maintenance therapy. The time required for relapse in all cases has varied from 1 month to 1 year. Patient 1 is the only patient who has remained in remission for more than a year after maintenance therapy has been discontinued. Patient 4 is in remission, but has only been observed for 8 months

since maintenance therapy was stopped. Both of these received 2 years of treatment before the drug in question was discontinued. Longer periods of observation are necessary before any conclusions can be drawn, since relapses have been described 2 years or more after completion of therapy.[18]

Maintenance therapy for adults who have exhibited a response to short-term therapy would seem to be indicated, on the basis of our results and those of Lange, if one would prevent relapses from occurring. However, the prevention of a relapse is not necessarily a justifiable reason for committing a patient to continuous treatment with large doses of potentially dangerous adrenal cortical steroid compounds if one has only to institute a short course of treatment to induce another remission. A more valid reason for maintenance therapy would be a decrease in the mortality rate in patients so treated. Investigations to date have failed to demonstrate any effect of short-term treatment on the mortality rate in childhood nephrosis.[3]

The effect of a scheduled program of steroid therapy administered for a given period of time (1 year or more) upon the mortality rate for this disease does indeed seem to be more favorable than the intermittent type of therapy for symptoms alone. Lange and associates[6] and Riley[19] have attempted to assess this problem statistically through the use of control (treatment of symptoms only or no treatment) and treated (scheduled maintenance therapy) groups. Observations have been made on children. The results obtained from this analysis seem to be valid, at least for children, and suggest that maintenance therapy does significantly prolong life.

One cannot apply the results in children to adults, however. Hypertension, vascular disease, pyelonephritis, and many other diseases that may directly or indirectly affect the kidney are more frequent in the adult and this fact must certainly affect the outcome of any renal disease in the adult, compared to the outcome of the same disease in the child. The duration of life in a child who develops nephrosis may be many years (patient 12, 16 years) in the absence of hormone therapy. If the disease develops in the fifth or sixth decade of life, the chances of survival for a given period of time are certainly less than in a child, regardless of the presence of nephrosis. If death in renal failure occurs in an adult with nephrosis and hypertensive cardiovascular disease, is this a death secondary to nephrosis or vascular disease? It would seem that the problem of determining the mortality rates in adults with nephrosis, treated and untreated, is a complex one which demands rigorous controls if statistically valid conclusions are to be drawn.

Our study does not contribute to the statistical evaluation of this problem. The 7 patients who did not receive maintenance therapy (8 through 13) cannot serve as controls for those who did (1 through 7)—5 of the 7 patients who received maintenance therapy demonstrated a response to short-term therapy; none of the untreated patients did. The average duration of disease (onset of edema) before treatment was under 4 months in the maintenance therapy group and averaged 28 months (extremes, 3 months and 12 years) in the other group. The average age of the maintenance therapy group was 30 years and that of the other group 49 years. It is evident that the two groups are not comparable.

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The striking difference in the two groups is, however, worthy of emphasis. The group that did not receive maintenance therapy has had a high mortality rate; the average time of observation for this group following the first short-term therapy is almost half of that of the group given maintenance treatment (36 months versus 53 months). Yet 5 have died, 1 has unchanged, advanced renal failure, and 1 has continued to have symptoms and signs of the nephrotic syndrome. Conversely, all of our patients who have received scheduled long-term treatment are, at the time of last observation, alive and completely well (5 patients) or are left with minimal proteinuria (2 patients) and no other signs or symptoms of the nephrotic syndrome. This observed difference in the treated (responsive) and untreated (nonresponsive) patients may be explained in the following ways: (1) The response to hormone therapy in adults with a nephrotic syndrome of unknown cause indicates a mild and reversible form of a single disease entity. Therapy prevents progression to a more severe, unresponsive state of the same disease and thus alters the mortality rate. (2) There are two or more disease entities represented in this series. One disease or group of diseases is unresponsive to steroid therapy and has a bad prognosis. The other disease or groups of diseases, although they respond to hormone therapy, have a good prognosis with or without therapy. Nephrotic syndromes with a good prognosis have been reported in adults.[20,21] In this instance the response to therapy would not affect the mortality. (3) The responsive group may, in the absence of hormone therapy, have a prognosis as bad as the unresponsive group. In this instance, as in the first, hormone therapy would be beneficial.

On the basis of longevity studies in children and the apparent benefit derived from long-term therapy in our patients, we would like to believe that hormone therapy does favorably influence the course of the nephrotic syndrome of unknown etiology in adults who have been demonstrated to be responsive to such therapy and who have been treated by means of scheduled therapy for a year or more. It must be emphasized, however, that lacking the natural history of the disease in patients responsive to therapy but untreated, no proof of prolonged survival in adults treated in this way is available.

This study suggests that all adult patients with a nephrotic syndrome of undetermined cause should receive a trial of hormone therapy to determine whether they will demonstrate a complete or partial response to such therapy. Duration of disease should not preclude a trial of therapy. Patients 1 and 2 had lapses of 3 and 4 years between treatment courses, were not in remission during that time, and yet responded well to treatment when they returned. Poor renal function does not preclude a response. The average of the urea clearances at the time of first observation was 43 per cent of normal in patients 1 through 7 and 40 per cent of normal in patients 8 through 13. Patient 5 had a urea clearance of 9 per cent of normal.

The histologic appearance of the glomeruli in a patient with the nephrotic syndrome may be of assistance in predicting the response of a given patient to treatment. The data are scarcely clear at present, however. Kark and coauthors[10] state that all of 11 patients with the nephrotic syndrome who showed normal glomeruli by light microscopy did well clinically. Some of these were given ACTH

or steroid compounds. Vernier and colleagues[22] have also observed such patients but describe clinical and histologic progression of the disease in some of these patients despite therapy. Galan and Maso,[7] on the other hand, did not encounter completely normal biopsy material in any of their pediatric cases and could not correlate the presence or absence of a response to treatment with the histologic appearance of the glomeruli.

Identification of adult patients who may benefit from prolonged hormone therapy is difficult. Some can be selected on the basis of their response to treatment of several weeks' duration—all those patients in this report who responded favorably to short-term treatment have had a continued remission while maintenance therapy was administered. The significance of a failure to respond to short-term hormone treatment is much less clear from our experience. Patients 6 and 7 exhibited no response to treatment of 2 or 3 weeks' duration. Patient 5 did not respond promptly at first but did eventually. The slow decrease in proteinuria and improvement in other parameters observed in patients 5, 6, and 7 in the course of prolonged treatment suggest that this treatment may have been beneficial. This response to prolonged therapy has been described but not emphasized by other investigators.[5,8] We believe this response should be emphasized. The possibility of a favorable response to prolonged treatment after the failure of an initial response to short-term therapy casts considerable doubt on the use of a brief course of hormone therapy to identify patients who will not benefit from therapy of longer duration. It extends the duration of treatment required before a negative result can be assumed to 3 or 4 months or more.

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SUMMARY AND CONCLUSION

Experience with 13 adult patients with a nephrotic syndrome of unknown etiology has been described. These patients were treated with adrenal corticotropic or adrenal cortical hormones.

Five patients demonstrated an unequivocal response to a short course of therapy (10 to 14 days). Two patients demonstrated a probable response only after therapy of more than 3 months' duration.

Four out of these 7 patients who responded to hormone therapy have relapsed after a short course of treatment on one or more occasions.

The same 4 out of 7 patients have relapsed after maintenance therapy has been discontinued, 1 of these after 2 years of maintenance therapy and the remainder after a minimum of 1 year of maintenance therapy. After further maintenance therapy, a complete remission without therapy has continued in 2 of these 4 patients for 3½ years, and 8 months, respectively.

The remaining 6 patients did not respond to one or more short courses of therapy and were not treated on a scheduled program of long-term therapy.

Adrenal cortical steroid hormones exert a beneficial effect on some adult patients with a nephrotic syndrome of unknown etiology. Prolonged treatment is necessary to ensure optimal results.

The authors wish to express their appreciation for the assistance given by Dr. Max Miller in initiating this study and for the kind cooperation of the many interns and residents involved in the study over the 5-year period. The technical assistance of Miss Therese M. Vargo has been invaluable. We are indebted to Dr. Simon Koletsky, Professor of Pathology, for interpretation of the pathologic material.

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APPENDIX

Clinical and Laboratory Observations, Before and After Treatment, on All Patients In The Study

PATIENT DESCRIPTION	DATE	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	ALBUMIN (GM. PER 100 ML. OF SERUM)	CHOLESTEROL (MG. PER 100 ML. OF SERUM)	UREA CLEARANCE (% NORMAL)	REMARKS
Patient 1—L.S. Age 26 White female Edema onset: February, 1950	Sept. 11, 1950	++	150/100	11.5	1.6	1,045	43	
	ACTH 25 mg. I. M. q. 6 hr. for 14 days (NR*)							
	Oct. 9, 1950	++	135/90	29.3	1.8	780	43	No specific program of Rx for 3 years
	Aug. 22, 1953	++++	140/90	3.2	1.9	632	40	
	ACTH 20 mg. I. V. q. d. for 11 days (R†)							
	Sept. 8, 1953	0	130/80	0	3.9	300	100	
	Maintenance Rx, cortisone 200 mg. q. d., decreased gradually							
	Aug. 23, 1955	0	155/110	0.27	4.3	179	75	Cortisone 50 mg. 3 days per week
	Steroid Rx stopped January, 1956. Reported to have blood pressure 154/100 and normal urinalysis March 6, 1959; normal pregnancy 1956							
Patient 2—L.G. Age 22 Negro male Edema onset: April, 1952	Aug. 19, 1952	+	150/100	9.3	1.4	629	20	
	ACTH 20 mg. I.V. q. d. for 15 days (R)							
	Sept. 5, 1952	0	180/105	2.5	2.0	395	60	Increased proteinuria 8 days after Rx
	Sept. 19, 1952	trace	130/85	10.3	1.7	560	—	
	Cortisone 25 mg. q. i. d. (R)							
	Oct. 7, 1952	0	130/85	0.4	3.0	462	117	Increase in proteinuria 9 days after Rx
	Jan. 30, 1953	+++	146/80	5.5	1.3	740	46	
	Cortisone 50 mg. q. d. for 18 days (NR)							

*NR = No decrease in urine protein excretion.

†R = Decrease in urine protein excretion.

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PATIENT DESCRIPTION	DATE	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	ALBUMIN (GM. PER 100 ML. OF SERUM)	CHOLESTEROL (MG. PER 100 ML. OF SERUM)	UREA CLEARANCE (% NORMAL)	REMARKS
Patient 2—(Cont'd)	Feb. 22, 1953	+++	146/80	7.3	1.7	585	60	
	Cortisone 50 mg. q. d. for 7 days, then b. i. d. for 4 days (NR)							
	March 4, 1953	0	135/90	6.5	1.6	585	—	Patient did not return for 1 year
	July 5, 1954	++	125/80	21.9	1.7	953	36	
	ACTH 20 mg. I. V. q. d. for 10 days (R)							
	July 16, 1954	++	125/80	4.6	2.0	795	50	Increase in proteinuria 9 days after Rx
	July 24, 1954	0	125/80	10.9	3.6	—	46	
	Depot ACTH 80 clinical units 3 days per week							
	March 5, 1955	0	138/84	++	3.1	—	50	
	Stopped Rx without orders May 22, 1955							
	May 25, 1956	+++	130/90	23.1	1.6	642	20	
	Prednisone 60 mg. q. d., decreased gradually							
	June 16, 1956	0	150/90	3.0	2.4	705	66	Prednisone 30 mg. q. d.
	Sept. 8, 1956	0	130/92	6.0	3.6	355	57	
	Patient lost from the study							
Patient 3—J.H. Age 28 White female Edema onset: October, 1954	Nov. 29, 1954	++	110/70	7.1	1.9	1,262	28	
	ACTH 25 mg. I. V. q. d. for 11 days (R)							
	Dec. 14, 1954	0	120/80	0	2.6	734	82	Increase in proteinuria 8 days after Rx
	Dec. 22, 1954	0	115/80	7.8	—	—	—	
	ACTH 25 mg. I. V. q. d. for 10 days (R)							

PATIENT DESCRIPTION	DATE	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	ALBUMIN (GM. PER 100 ML. OF SERUM)	CHOLESTEROL (MG. PER 100 ML. OF SERUM)	UREA CLEARANCE (% NORMAL)	REMARKS
Patient 3—(Cont'd)	Jan. 3, 1955	0	110/80	0	3.6	314	55	
	Depot ACTH 80 clinical units 3 days per week							Increase in proteinuria 2 months later
	March 11, 1955	++	110/60	8.6	1.6	890	55	
	ACTH 25 mg. I. V. q. d. for 10 days (R)							
	March 25, 1955	0	140/60	0	2.6	684	49	Increase in proteinuria 9 days after Rx despite depot ACTH 80 clinical units
	April 6, 1955	0	120/80	7.4	2.6	659	70	
	ACTH 25 mg. I. V. q. d. for 10 days (R)							
	April 21, 1955	0	130/90	0	3.7	338	54	
	Maintenance Rx, prednisone 30 mg. q. d. Dose gradually decreased to 40 mg. 3 days per week by May 16, 1955							
	May 25, 1955	0	—	10.5	—	—	—	
	Prednisone increased to 50 and then 60 mg. q. d.							
	June 16, 1955	0	135/85	3.5	2.8	534	83	
	ACTH 25 mg. I. V. q. d. for 10 days (R)							
	June 29, 1955	0	130/80	0	3.3	306	58	
	Maintenance Rx, prednisone 60 mg. q. d. and decreased gradually							
	Oct. 3, 1955	0	130/80	0	4.4	315	79	Dose 40 mg. q. d.
	Prednisone decreased to 37.5 mg. by Oct. 5, 1955							
	Oct. 8, 1955	0	—	0.65	—	—	—	
	Prednisone 40 mg. q. d.; daily 24-hour urine collection Oct. 8 to 14, 1955							

PATIENT DESCRIPTION	DATE	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	ALBUMIN (GM. PER 100 ML. OF SERUM)	CHOLESTEROL (MG. PER 100 ML. OF SERUM)	UREA CLEARANCE (% NORMAL)	REMARKS
Patient 3—(Cont'd)	Oct. 9, 1955	0	145/100	0.8	—	332	—	
	Oct. 13, 1955	0	120/90	0	—	—	—	
	April 23, 1956	0	120/80	0	—	—	—	Prednisone decreased gradually
	Prednisone decreased to 40 mg. 4 days per week by April 24, 1956							
	May 7, 1956	0	120/90	2.1	—	—	—	
	Prednisone 60 mg. q. d. and decreased gradually							
	May 22, 1956	0	130/78	0	—	—	—	
	Jan. 1, 1957	0	150/70	0	4.7	234	84	Prednisone 35 mg. q. d.
	March 11, 1957	0	145/90	0	—	—	—	Prednisone 15 mg. q. d.
	Prednisone 10 mg. q. d.							
	April 15, 1957	0	145/110	2.0	—	—	—	
	Prednisone 20 mg. q. d.							
	April 22, 1957	0	—	0	—	—	—	
	May 7, 1957	0	150/98	0	—	—	—	
	Prednisone 15 mg. q. d.							
	May 21, 1957	0	—	0.6	—	—	—	
	Prednisone 20 mg. q. d.							
	June 1, 1957	0	—	4.1	—	—	—	
Patient 4—E.H. Age 29 White female Edema onset: October, 1953	April 15, 1954	++++	140/90	7.6	1.3	940	60	Rx attempted elsewhere without success
	ACTH 20 mg. I. V. q. d. for 10 days (R)							

PATIENT DESCRIPTION	DATE	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	ALBUMIN (GM. PER 100 ML. OF SERUM)	CHOLESTEROL (MG. PER 100 ML. OF SERUM)	UREA CLEARANCE (% NORMAL)	REMARKS
Patient 4—(Cont'd)	April 27, 1954	++	110/80	1.3	2.8	585	70	Increased proteinuria 4 days after Rx
	Aug. 18, 1954	++++	110/80	12.0	1.2	910	25	
	ACTH 20 mg. I. V. q. d. for 10 days (R)							
	Aug. 29, 1954	++	130/90	0.9	2.7	578	42	Increased proteinuria 3 days after Rx
	ACTH 20 mg. I. V. q. d. for 10 days (R)							
	Sept. 24, 1954	0	120/75	0.2	3.2	403	60	
	Maintenance Rx, depot ACTH 80 clinical units 3 days per week							
	April 12, 1956	0	118/82	0	4.6	246	64	
	Stopped maintenance April 12, 1956; increased proteinuria 2 months later							
	June 19, 1956	0	116/72	1.7	3.2	199	40	
	Prednisone 40 mg. q. d.							
	July 5, 1956	0	108/70	0	2.9	280	—	
	Dose decreased and stopped by Dec. 4, 1958 without a relapse; April 12, 1956, through Dec. 4, 1958, acute purulent sinusitis, measles, and mumps were observed without relapse							
	Feb. 20, 1959	0	94/58	0	3.7	112	80	
Patient 5—D.S. Age 45 Negro female Edema onset: October, 1953	Dec. 10, 1953	++	150/80	9.8	1.4	—	9	
	ACTH 20 mg. I. V. q. d. for 12 days (R)							Proteinuria did not decrease until 11 days after Rx
	Jan. 5, 1954	++	180/120	2.3	—	—	30	
	Jan. 25, 1954	0	160/80	—	1.9	—	54	
	April 1, 1954	+++	170/86	12.6	1.4	592	16	
	Hydrocortisone 20 mg. q. i. d. for 11 days (NR)							

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PATIENT DESCRIPTION	DATE	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	ALBUMIN (GM. PER 100 ML. OF SERUM)	CHOLESTEROL (MG. PER 100 ML. OF SERUM)	UREA CLEARANCE (% NORMAL)	REMARKS
Patient 5—(Cont'd)	April 21, 1954	+++	130/80	24.1	1.3	769	—	
	ACTH 20 mg. I. V. q. d. for 10 days (R)							
	May 3, 1954	+++	120/80	5.0	1.3	—	28	Increase in proteinuria 4 days after Rx
	Depot ACTH 80 clinical units 3 days per week							
	Feb. 2, 1955	0	140/90	0.9	3.7	280	83	
	July 27, 1956	0	120/85	0	3.9	281	58	
	Discontinued Rx							
	Dec. 21, 1956	0	140/90	0.4	3.5	234	63	
	May 3, 1957	0	150/90	1.3	—	—	—	
	Prednisone 40 mg. q. d. and decreased gradually; discontinued ACTH							
	June 21, 1957	0	140/90	0.7	—	—	—	Prednisone 20 mg. q. d.
	July 12, 1957	0	150/95	0	—	—	—	Prednisone 15 mg. q. d.
	July 15, 1957	0	150/90	0.5	—	—	—	
	Prednisone 20 mg. q. d.							
	Aug. 2, 1957	0	150/95	3.0	—	—	—	
	Prednisone 40 mg. q. d. and decreased gradually							
	June 30, 1957	0	154/94	0	—	—	—	
	Oct. 11, 1957	0	154/100	0	4.1	305	117	
	Prednisone to 10 mg. q. d.							
	Nov. 15, 1957	0	154/100	0.4	—	—	—	
	Prednisone increased to 20 mg. q. d.							

PATIENT DESCRIPTION	DATE	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	ALBUMIN (GM. PER 100 ML. OF SERUM)	CHOLESTEROL (MG. PER 100 ML. OF SERUM)	UREA CLEARANCE (% NORMAL)	REMARKS
Patient 5—(Cont'd)	Feb. 17, 1958	0	150/100	4.9	—	—	—	
	Prednisone increased to 40 mg. q. d. and decreased gradually							
	March 21, 1958	0	155/102	0	—	—	—	Prednisone 25 mg. q. d.
	July 8, 1958	0	150/98	0	4.1	289	116	Prednisone 20 mg. q. d. since April 4, 1958
	Aug. 1, 1958	0	150/98	1.4	—	—	—	
	Prednisone increased to 40 mg. q. d. and decreased gradually							
	Aug. 15, 1958	0	150/120	0	—	—	—	Prednisone 30 mg. q. d.
	Oct. 16, 1958	0	150/100	0	—	—	—	
	Prednisone decreased to 15 mg. q. d.							
	Oct. 30, 1958	0	150/100	1.5	—	—	—	
	Prednisone increased to 25 mg. q. d. and not changed							
	Nov. 20, 1958	0	150/100	0.5	—	—	—	
	Feb. 12, 1959	0	150/100	0.4	4.4	260	80	
	Course unchanged to present; 25 mg. q. d. of prednisone is accompanied by minimal proteinuria but not a complete remission as with the dose at 40 mg. q. d.							
Patient 6—J.M. Age 28 White male Edema onset: August, 1957	Nov. 28, 1957	++	140/85	11.2	2.2	492	78	
	Prednisone 80 mg. q. d. to March 11, 1958; aliquots of daily 24-hour urine obtained to present							
	March 11, 1958	0	130/98	4.4	4.0	—	—	
	Prednisone 70 mg. q. d. and decreased gradually; stopped July 29, 1958							
	July 29, 1958	0	140/85	1.9	—	—	—	
	March 18, 1958	0	135/85	1.0	4.0	—	99	
	To date patient remains well with minimal proteinuria and no Rx							

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PATIENT DESCRIPTION	DATE	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	ALBUMIN (GM. PER 100 ML. OF SERUM)	CHOLESTEROL (MG. PER 100 ML. OF SERUM)	UREA CLEARANCE (% NORMAL)	REMARKS
Patient 7—B.D. Age 29 Negro female Edema onset: July, 1954	Aug. 1, 1954	++++	120/70	4.0	1.0	884	65	
	ACTH 25 mg. I. V. q. d. for 9 days (NR)							Human serum albumin 225 Gm.
	Aug. 23, 1954	+++	110/60	2.2	1.0	740	—	
	Depot ACTH 50 clinical units 3 days per week							
	Sept. 26, 1954	++	120/70	3.6	0.9	950	—	
	ACTH 25 mg. I. V. q. d. for 10 days (NR)							Human serum albumin 350 Gm.
	Oct. 15, 1954	+	120/70	56.2	2.3	—	—	
	ACTH 40 mg. I. V. q. d. for 10 days (NR)							
	Nov. 7, 1954	+	110/70	6.8	1.1	—	56	
	Depot ACTH 80 clinical units 3 days per week; discontinued by error Nov. 26, 1954							
	Jan. 19, 1955	++	112/70	4.4	1.7	621	55	
	ACTH 40 mg. I. V. q. d. for 10 days (NR)							
	Feb. 8, 1955	++	116/70	5.8	1.5	450	60	
	Depot ACTH 80 clinical units 3 days per week							
	Sept. 16, 1955	0	118/74	0.5	3.4	204	38	
	Dec. 30, 1955	0	104/60	2.2	—	—	—	Pregnant
	Feb. 22, 1956	0	120/65	0.5	2.6	—	92	
	April 11, 1956	0	120/80	2.1	2.2	—	—	
	Depot ACTH 80 clinical units q. d.							
	May 9, 1956	0	150/90	5.6	2.6	332	49	
	Change to prednisone 50 mg. q. d.							Spontaneous delivery, stillborn

PATIENT DESCRIPTION	DATE	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	ALBUMIN (GM. PER 100 ML. OF SERUM)	CHOLESTEROL (MG. PER 100 ML. OF SERUM)	UREA CLEARANCE (% NORMAL)	REMARKS
Patient 7—(Cont'd)	May 23, 1956	0	130/90	4.2	2.9	—	—	
	Increase prednisone to 80 mg. q. d.							
	May 28, 1956	0	130/90	5.0	3.4	545	—	
	June 15, 1956	0	140/85	4.4	2.9	—	51	
	Decrease prednisone to 70 mg. q. d.							
	June 29, 1956	+	170/110	4.9	—	760	55	
	Decrease prednisone to 40 mg. q. d.							
	Aug. 20, 1956	++	152/102	12.2	2.5	640	51	
	Sept. 3, 1956	+++	160/100	4.2	2.2	532	—	
	Depot ACTH 80 clinical units 3 days per week							
	Dec. 28, 1956	0	150/90	3.4	—	—	—	
	July 19, 1957	0	130/76	0.6	—	—	—	Pregnant
	Aug. 23, 1957	0	130/76	1.1	—	—	—	
	Aug. 27, 1957	0	130/80	++++	3.0	152	—	Therapeutic abortion, renal biopsy, tubal ligation
	Dec. 30, 1957	0	130/75	0.43	3.5	152	77	
	June 6, 1958	0	114/70	0.83	—	—	—	
	Stopped Rx							
	Sept. 30, 1958	0	110/70	0.8	3.5	171	76	
	March 9, 1959	0	112/72	1.1	3.9	165	58	
Patient 8—I.D. Age 69 Negro female Edema onset: December, 1957	March 1, 1958	++	150/65	4.1	2.1	468	24	Sudden death June 17, 1959, due to coronary occlusion, myocardial infarction, and ventricular rupture
	Prednisone 50 mg. q. d. for 10 days (NR)							
	Nov. 6, 1958	+	210/110	10.0	2.2	—	25	

PATIENT DESCRIPTION	DATE	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	ALBUMIN (GM. PER 100 ML. OF SERUM)	CHOLESTEROL (MG. PER 100 ML. OF SERUM)	UREA CLEARANCE (% NORMAL)	REMARKS
Patient 9—T.C. Age 55 Negro male Edema onset: October, 1954	June 28, 1955	++++	200/110	7.5	2.3	364	27	
	Prednisone 60 mg. q. d. for 15 days (NR)							Diuretics and human serum albumin
	Aug. 22, 1951	0	150/80	4.0	2.6	—	—	
	Sept. 10, 1958	++	140/95	++	3.9	206	24	
Patient 10—M.B. Age 65 Negro male Edema onset: February, 1950	Feb. 10, 1951	++	170/85	8.3	2.4	618	68	
	ACTH 25 mg. I. M. q. 6 hr. for 10 days (NR)							
	Feb. 22, 1951	++	130/80	9.4	2.2	—	—	Died Dec. 14, 1955
Patient 11—G.S. Age 48 White male Edema onset: October, 1956	Nov. 12, 1957	++	130/80	6.7	2.1	500	85	
	Prednisone 50 mg. q. d. for 17 days, 80 mg. for 8 days, decreased and stopped 8 days (NR)							
	Feb. 17, 1958	++	120/80	5.4	1.6	745	91	
	ACTH 40 mg. I. V. q. d. for 21 days (NR)							
	March 21, 1958	+	120/80	5.2	1.8	564	—	
Patient 12—D.D. Age 22 White female Edema onset: 1943	March 11, 1955	0	130/90	4.3	2.3	525	32	
	ACTH 20 mg. I. V. q. d. for 10 days (NR)							
	Sept. 7, 1955	+	154/72	3.4	2.2	369	28	
	Oct. 26, 1956	0	190/130	3.3	2.8	—	19	
	April 25, 1957	0	190/130	5.7	3.3	272	9	
	Jan. 31, 1958	0	202/128	2.0	3.4	177	5	Died

PATIENT DESCRIPTION	DATE	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	ALBUMIN (GM. PER 100 ML. OF SERUM)	CHOLESTEROL (MG. PER 100 ML. OF SERUM)	UREA CLEARANCE (% NORMAL)	REMARKS
Patient 13—E.N. Age 36 White male Edema onset: May, 1954	March 28, 1955	+	140/70	13.2	2.9	380	23	
	ACTH 25 mg. I. V. q. d. for 10 days (NR)							
	April 12, 1955	+	140/70	30.0	2.7	—	28	
	Prednisone 40 mg. q. d. for 11 days (NR)							
	Dec. 28, 1956	++	170/90	++++	3.4	—	—	Sudden death at home; no autopsy

THE USE OF Na^{22} TO STUDY THE SODIUM-RETAINING PROPERTIES OF STEROID THERAPY IN RHEUMATOID ARTHRITIS

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THE value of long-continued hormone therapy in certain cases of severe rheumatoid arthritis and other collagen diseases is no longer in doubt.[5] However, dosage of cortisone in amounts adequate to control disease activity (e.g., in disseminated lupus erythematosus) may be impossible because of sodium retention. Prednisone and prednisolone are potent glucocorticoids with relatively few sodium-retaining properties,[4,10,11] although they still have other undesirable side effects. With the development of newer steroids, it was thought worth while to record the application of the technique of whole body counting with Na^{22}, as described by Veall and co-workers,[14] to follow the body sodium over a period of weeks. By this method, it was possible to evaluate the relative sodium retention during cortisone and prednisolone therapy.

MATERIAL AND METHODS

The study was carried out on hospitalized patients with rheumatoid arthritis for whom hormone therapy had been prescribed.

Throughout the study they received a regular and constant amount of analgesics and physiotherapy. The diet was individualized so that the total caloric content was 150 per cent of their calculated basic requirements and was composed of protein, 1.25 Gm. per kilogram body weight (75 per cent from animal sources), fat up to 30 per cent of the total calories, and the remainder made up of carbohydrates. The diet itself contained 800 mg. sodium and was supplemented to a total of 3 Gm. (130 mEq.) daily by the addition of sodium chloride capsules.

Work performed during tenure of at C. J. Adams Fellowship.

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TABLE I. CLINICAL DATA AND ISOTOPE RESULTS

PATIENT	SEX	AGE	DURATION OF STUDY (DAYS)	STEROID THERAPY	BODY WEIGHT			TOTAL EXCHANGEABLE BODY SODIUM				BIOLOGIC HALF-LIFE* OF Na^{22} (DAYS)		
					BASAL AVERAGE (KG.)	CHANGE DURING THERAPY		BASAL AVERAGE (MEQ./KG.)	BASAL AVERAGE (EQ.)	CHANGE DURING THERAPY		BASAL	ΔF†	E‡
						ΔF† (KG.)	E‡ (KG.)			ΔF† (EQ.)	E‡ (EQ.)			
Healthy control														
W.W.	M	28	32		73.2	—	—	37.1	2.72	—	—	10	—	—
Short-term steroid therapy														
W.K.	M	59	20	Basal 10 days, 50 mg. ΔF for 10 days.	79.5	−2.2		40.3	3.20	−.20		16	15	
			20	Basal 6 days, 200 mg. E for 10 days.	76.2		+1.8	42.2	3.22		+.28	16		32
F.R.	M	55	26	Basal 5 days, 200 mg. E for 9 days.	61.7		+0.9	43.7	2.70		+.24	10		19
			20	Basal 5 days, 50 mg. ΔF for 9 days.	62.0	−2.0		42.8	2.70	−.10		11	12	
E.M.	F	67	28	Basal 6 days, 75 mg. E for 22 days, plus added 50 mg. ΔF for 7 days.	50.8		+0.7	41.3	2.10		+.50	10		17
			27	Basal 6 days, 50 mg. ΔF for 21 days, plus added 75 mg. E for 7 days.	51.1	−0.7		41.0	2.10	−.30		10	12	
Maintenance steroid therapy														
E.F.	F	61	23	Basal 3 days, 20 mg. ΔF for 20 days.	58.4	−2.5		40.5	2.37	−.39		10	10	
J.W.	F	47	30	Basal 5 days, 75 mg. E for 25 days.	45.8		+2.8	40.5	1.86		+.34	9		15
			27	E for 6 months, then 75 mg. E for 14 days, changed to 15 mg. ΔF for 13 days.	§57.6	−1.8		§39.6	§2.28	−.38		§14	12	
E.S.	M	55	20	E for 6 months, then 150 mg. E for 9 days, changed to 30 mg. ΔF for 10 days.	§66.3	−2.6		§48.2	§3.20	−.34		§15	9	

*Time calculated from slope of Na^{22} decay curve for theoretically half the dose to be excreted for the particular conditions.
†ΔF = prednisolone.
‡E = cortisone.
§Maintenance cortisone therapy for 6 months prior to Na^{22} administration.

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Fluids were allowed as desired with measurement of the 24 hour intake and urinary output. Daily weights were obtained before breakfast at the same time each day.

A single tracer dose of Na^{22} (15 to 20 μc) was given orally and 12 hours allowed for equilibration before any measurements were taken. Serial determinations of the biologic decay rate of Na^{22} were made daily at the same time each morning, with a total body counter with 8 matched Geiger-Muller tubes.[14] The counter was calibrated daily against an equivalent dose to provide an individual calibration value for each patient, thus automatically correcting for radioactive decay. The counting error for duplicate and triplicate counts (each 40,000 minimum) was 1 per cent. Replicate counts during a one hour period, with the patient positioned and motionless, had a deviation of 1.5 per cent. The dose of radiosodium, less than one-third the permissible dose, enabled measurements to proceed for more than 30 days.

Within one hour of the measurement of total body radioactivity, a "spot" specimen of urine was obtained for estimation of specific activity from Na^{22} (EKCO liquid sample scintillation counter) and Na^{23} (EEL flame photometer) contents. The total exchangeable sodium was calculated from the remaining body radioactivity/specific activity of urine. The total calculated variation for exchangeable sodium was 3.6 per cent.[2]

Following a control time period for the determination of the basal trend of the biologic decay curve, either cortisone or prednisolone was administered and various comparisons made.

RESULTS

The clinical data and isotope results are presented in Table I.

1. Healthy Controls.—Fig. 1 presents a typical result of the decay curve of Na^{22} total body activity in a healthy male. The biologic half-life was 10 days, and the total exchangeable sodium and body weight showed small fluctuations during the 32 day period. These results were similar to those previously reported.[1,14] With a low sodium intake (1 Gm. per day) or retention or edema, the slope of the decay curve decreased owing to slower turnover, while with increased sodium intake and/or excretion, the faster turnover accelerated the slope of the decay curve.

2. Short-Term Steroid Therapy.—Cortisone and prednisolone were administered separately in moderately large doses to the same patient over short periods; in one patient the effect of the addition of the other steroid for 7 days during the treatment period was studied. The following case reports illustrate the effect of steroid therapy on sodium metabolism:

Case reports: W. K., a 59-year-old man, suffered from generalized rheumatoid arthritis for 6 years and at this time had marked edema of the feet and legs. Prednisolone, 50 mg. per day for 10 days, caused marked clinical improvement with loss of ankle edema and 2.2 kilograms in weight. There was no significant effect on the biologic decay rate (Fig. 2). Six days after prednisolone was stopped, when the joints were again very painful and swollen but without edema

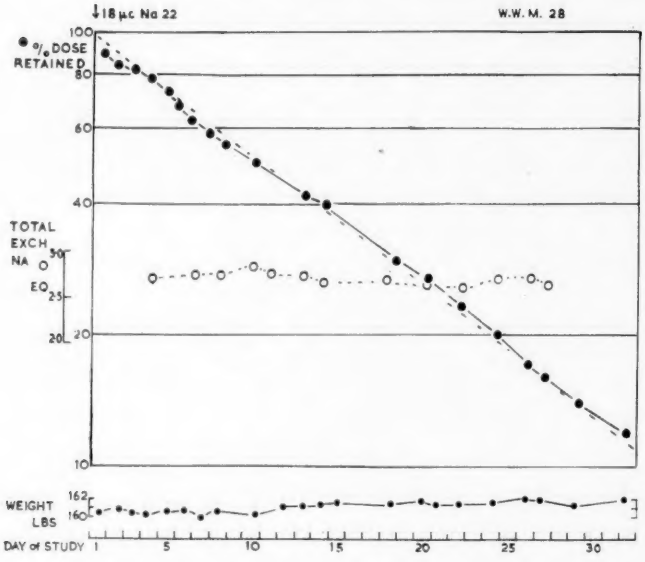

Fig. 1.—The biologic decay curve (per cent of Na^{22} dose retained) and total exchangeable sodium (in Eq.) in a healthy male subject.

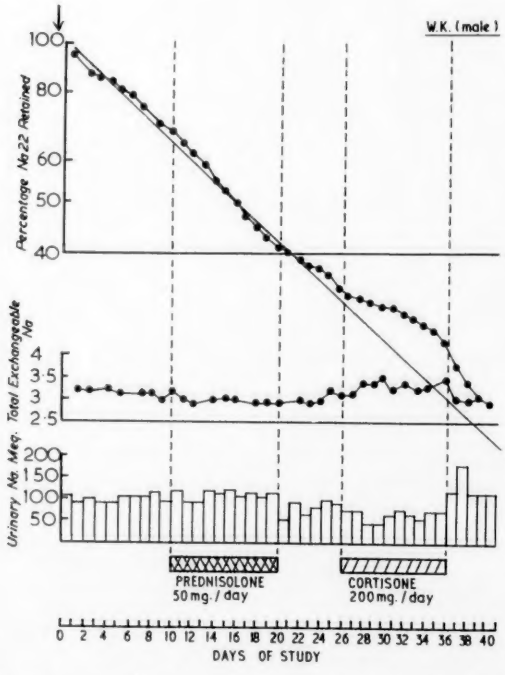

Fig. 2.—Patient W. K. Comparison of short-term administration of prednisolone and cortisone on the decay curve, total exchangeable sodium (in Eq.) and daily urinary sodium output (in mEq.). Sodium intake was 130 mEq. per day.

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cortisone was commenced, 200 mg. per day. An excellent clinical response followed, but there was a marked slowing of the biologic decay rate of Na^{22}, associated with a rise in weight and total exchangeable sodium and return of edema in the absence of active arthritis. When cortisone was discontinued, the biologic decay rate rapidly returned toward the basal rate of decay with a fall in total exchangeable sodium. The 24 hour urinary output of sodium rose slightly during prednisolone therapy and fell slightly below the control levels after therapy. During cortisone treatment, there was a marked reduction in urinary sodium excretion which rose above control levels when cortisone was stopped. Variations in fluid balance followed the fluctuations in body weight, urinary sodium, and total exchangeable sodium.

F. R., a man aged 55, had suffered from generalized rheumatoid arthritis for 15 years. The administration of cortisone, 200 mg. per day for 9 days, caused an increase in body weight and sodium retention (Table I). Withdrawal of cortisone led to a reversal of these features and diuresis. When the patient had had a clinical relapse, 12 days after cortisone was stopped, a further dose of Na^{22} was given. After a suitable time interval prednisolone, 50 mg. per day, was given for 9 days. This was not associated with any apparent effect on the Na^{22} decay rate, but there was a slight fall in total exchangeable sodium and a 2 kilogram loss in weight.

E. M., was a 67-year-old woman with severe rheumatoid arthritis for 6 years. Cortisone, 75 mg. per day, caused a marked delay in the Na^{22} decay rate with a rise in total exchangeable sodium (Fig. 3). The addition of prednisolone, 50 mg. per day for 7 days, appeared to cause sodium diuresis, in that the decay curve for total body activity returned to a more uniform pattern and total exchangeable sodium to pretherapy levels. In a second study, when the patient was maintained on prednisolone, there was minimal slowing of the Na^{22} decay rate for the first 7 days, but when cortisone was introduced in addition, it exerted its sodium-retaining capacity with a rise in total exchangeable sodium, which fell to less than pretherapy levels on discontinuance of cortisone, despite continuation of prednisolone (Fig. 3).

Comment: These reports indicate that there is good agreement between the metabolic and isotope studies, with close correlation between the trends in the slope of body Na^{22} retention and total exchangeable sodium, and the urinary sodium, fluid balance, and body weight. The technique provides a practical method of following sodium balance and the changes in total body weight reflecting the edema associated with sodium retention.

3. Maintenance Steroid Therapy.—Maintenance therapy confirmed the results of short-term treatment, viz., that prednisolone has a lesser tendency to produce sodium retention than cortisone. The clinical effect of prednisolone was as good as that for cortisone (Table I).

Case report: J. W., a 47-year-old woman, had had severe rheumatoid arthritis for 5 years. Administration of cortisone, 75 mg. per day, caused a marked slowing in turnover of sodium, as shown by the slow fall in total body activity with rise in total exchangeable sodium and body weight (Fig. 4; compare the case of E. F. on maintenance prednisolone).

On maintenance therapy with cortisone for the next 6 months, J. W. gradually developed ankle edema, which was not adequately controlled by sodium restriction. Readmitted to the hospital, she was kept on the prescribed diet and cortisone, 75 mg. per day, before the Na^{22} was given. The fall in total body activity was slower than anticipated from the previous basal level without hormone, but replacement with prednisolone, 15 mg. per day, on the fourteenth day resulted in a marked fall in total body activity for 4 days, followed by a more rapid decay rate than while on cortisone. This was accompanied by a fall in total exchangeable sodium to the level of her pre-hormone state, loss of weight, and reduction in edema. E. S., after 6 months on cortisone, 150 mg. per day, and with ankle edema despite a salt-free diet, showed a similar response in sodium metabolism and loss of edema on changing to prednisolone (Fig. 5).

DISCUSSION

With radioactive elements possessing a long physical half-life, the reduction by half in the radio element due to excretion gives the biologic half-life of the regular element. Utilizing this principle for Na^{22}, Threefoot and associates[13] pointed out that there was a wide variation due to diet, environment, and physical activity. Hence, our patients were placed on routine daily physiotherapy and a standard diet with 3 Gm. sodium per day to prevent undue irradiation and to maintain a moderately fast turnover. In these circumstances, it was considered that any change in sodium turnover rate could be attributed to hormone administration.

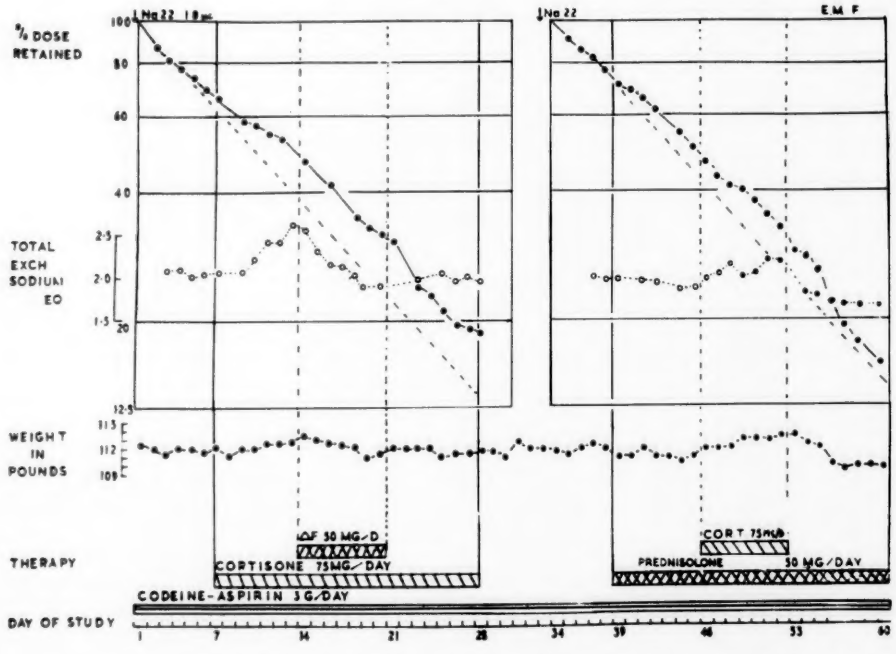

Fig. 3.—Patient E. M. Influence of one steroid on the decay curve and total exchangeable sodium produced by the other steroid.

Wilson and his collaborators,[15] comparing metabolic balance studies and isotopic dilution (K^{42} and Na^{24}) methods, found the isotopic technique as accurate and easier for serial determinations of total exchangeable sodium over a long period. Similarly, Martin and Walker[7] reported that the biologic half-life of Na^{22} depended on the sodium intake and equilibration of Na^{22} with the exchangeable body sodium required 72 hours. When these factors were taken into consideration, there was close agreement between metabolic balances and isotopic studies. Our results are in close agreement with theirs.

The use of the total body counter obviated the necessity for estimating all isotopic losses, especially extrarenal, as required by the long-term classical studies.

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After initial equilibration of the oral isotope (Miller and Wilson[9] found no difference in results by the oral or intravenous route), continuous estimation of isotope losses was unnecessary, since the specific activities of "spot" urines were found sufficiently accurate.[2,7] The biologic half-life of Na^{22} for normal subjects on a 3 Gm. sodium intake per day was 10 to 14 days, and the basal (actual or calculated) half-life for the patients was 9 to 16 days. Deviations were readily detected, e.g., errors in salt intake; unreported vomiting, diarrhea, sweating, etc.; and the effect of sodium and/or potassium deprivation or supplement. Since the results of Edelman and co-workers[6] and Miller and associates[8] suggest caution in the use of Na^{22} because of deposition on bone surfaces and in growing bone, the

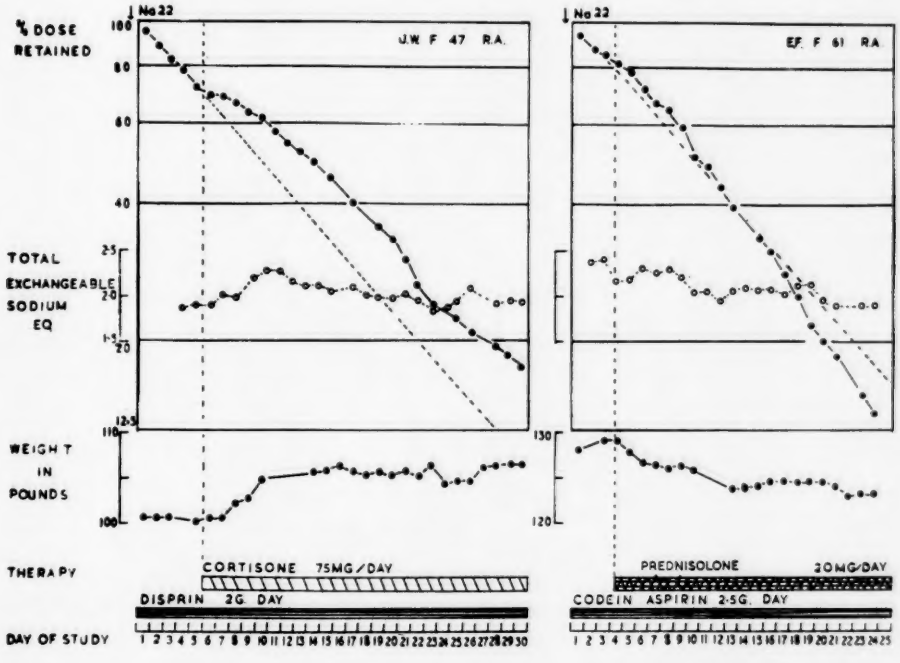

Fig. 4.—Sodium retention during cortisone, but not during prednisolone therapy.

doses used were less than those used by other investigators, while patients were restricted to an older group. The use of Na^{24} presents some disadvantages because of its very short physical half-life and lower detection efficiency.

Despite the simplicity of the technique, a major difficulty occurred in young women, in that a tendency to sodium retention in relation to menstruation[12] prevented satisfactory interpretation of changes about this time.[1] We have therefore restricted this report to postmenopausal women. Several other difficulties were also encountered. Diarrhea and vomiting in one case necessitated rejection of the data. Patients maintained on a low sodium intake had small sodium turnover and less satisfactory decay curves. Finally, an occasional very low

urinary sodium (both chemical and radioactive), e.g., during the retention phase of cortisone therapy, tended to increase the error of estimation and consequently the total exchangeable sodium for that day.

The administration of 75 to 200 mg. cortisone per day caused sodium retention and a rise in total exchangeable sodium and body weight; with prednisolone, in doses up to 50 mg. per day, sodium retention did not occur, and all cases tended to show a slight fall in total exchangeable sodium and body weight (Table I). The administration of prednisolone, once sodium retention had occurred on cortisone therapy, was followed by a sharp increase in Na^{22} decay rate, associated

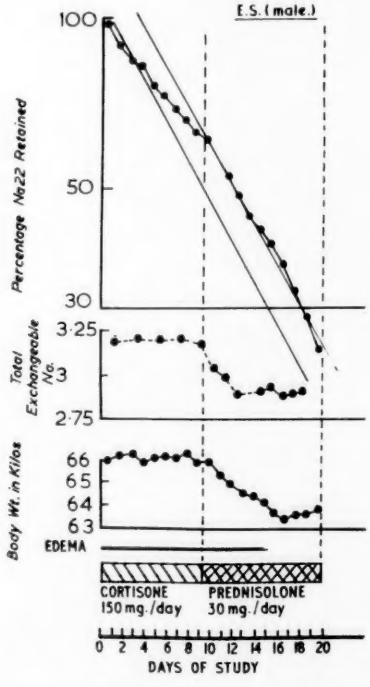

Fig. 5.—Patient E. S. Loss of cortisone edema and sodium retention on being transferred to prednisolone therapy.

with a fall in total exchangeable sodium and sodium diuresis, and subsequently with loss of edema (Patients E. M., J. W., and E. S.). The absence of sodium retention with prednisolone is in agreement with the findings of other workers,[3,4,11] as is the loss of cortisone edema when patients are changed to prednisolone.[10]

SUMMARY

1. Following the oral administration of Na^{22}, the biologic decay of sodium and the total exchangeable sodium were followed with the use of a total body counter and a single daily urine sample. This proved to be a satisfactory method for studying the trend in body sodium.

2. The administration of cortisone, 75 to 200 mg. per day, to patients with long-standing rheumatoid arthritis, was associated with sodium retention, which did not occur with prednisolone in the dose range of 15 to 50 mg. per day. Fluid accumulation, evidenced by a rise in body weight, accompanied the sodium retention.

3. Prednisolone had a natriuretic effect in certain situations.

We wish to thank Professor E. G. L. Bywaters for allowing us access to his patients, Professor E. J. King and Dr. C. E. Dalgleish for laboratory facilities, and Dr. J. E. S. Bradley for his advice on the application of Na^{22} in this study.

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THE ANALGESIC POTENCY OF PIMINODINE (ALVODINE)

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PIMINODINE or WIN-14, 098-2 (ethyl-4-phenyl-1-(3-phenylaminopropyl) piperidine-4-carboxylate ethanesulfonate) is structurally similar to meperidine, differing in that 3 (phenyl-amino) propyl replaces a methyl group on the nitrogen atom of the piperidine ring. It was synthesized by Elpern[1] and tested for analgesic potency by Grumbach[2] in the laboratories of the Sterling Winthrop Research Institute. Its structure is depicted below. Unpublished data suggested that the analgesic activity of piminodine as determined by the D'Amour-Smith, rat-tail, radiant heat technique, was 8.8 times as great as that of meperidine hydrochloride and 1.5 times as great as that of morphine sulfate.

The present study was undertaken to determine the analgesic potency of piminodine utilizing patients suffering from postoperative pain.

METHODS

Patients were selected from the surgical wards of the Baltimore City Hospitals, and ranged in age from 15 to 64 years with a mean age of 36 years. Sixty-eight females and 28 males constituted the total sample. The types of operations included: hysterectomy, herniorraphy, appendectomy, lobectomy, cholecystectomy, vein stripping, hemorrhoidectomy, suprapubic prostatectomy, and a variety of orthopedic procedures.

The patients were selected by one physician (T. J. DeK.), who wrote orders for pain relief, prescribing alternate doses of subcutaneous medication, identified only by code letters. In the first group of patients, 10 mg.* of morphine was alternated with 5 mg.* of piminodine. In the second and third groups of patients,

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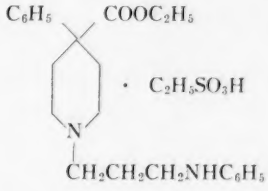
*The weights refer to the salts of the analgesic compounds.

10 mg.* of morphine was alternated with 10* and 20* mg. of piminodine, respectively. In approximately half of the patients in any group the standard (morphine) was administered first and in the other half of the patients the experimental drug was given first. Neither patients nor interviewing technicians were aware of the nature of the medications. Medication was administered only on request of the patient for pain relief, and no medication could be given less than 2 hours after the preceding medication. Patients were interviewed prior to injection and at intervals of ½, 1, 2, 3, and 4 hours after injection. At these interviews, patients were awakened if necessary and asked to categorize their pain as absent, slight,



Piminodine ethanesulfonate
(WIN-14, 098-2)

moderate, severe, or very severe. A decrease in pain from predrug level to the next level was counted as a score of plus 1, a drop of two levels as plus 2, etc. If no change occurred a score of zero was given, and if pain increased over the predrug level (a relatively rare phenomenon) a negative score was given. If a medication was administered less than 4 hours after a previous medication, scores of zero were automatically counted for whatever interviews were thus ruled out for the earlier drug.

RESULTS

The data are presented in a variety of ways, as described in an earlier publication[3]:

Mean Pain Relief Scores for All Doses Administered (*Table I*).—Here each dose contributes equally to the score, but some patients contribute considerably more than others, since the number of doses administered to a given patient varied from 1 to 6. Notice that in all 5 tables the performance of 10 mg. of morphine surpasses that of 5 mg. of piminodine, whereas it is inferior to the performance of 10 and 20 mg. of piminodine.

Mean "Individual" Pain Relief Scores (*Table II*).—Here each patient contributes equally to the total score, since a mean score is computed for each interview point for each drug for each patient (regardless of how many times the drug was given) and then a mean of these average scores is calculated.

Mean Pain Relief Scores for First Doses Only (*Table III*).—The purpose of this score is to eliminate possible order effects.

Incidence of Complete Pain Relief (*All Doses*) (*Table IV*).—The percentage of doses providing complete relief at the various time intervals is shown.

*The weights refer to the salts of the analgesic compounds.

TABLE I. MEAN PAIN RELIEF SCORES (ALL DOSES)

DRUG	HOURS AFTER MEDICATION				
	½	1	2	3	4
Morphine 10 mg. N = 34 doses	0.95	2.12	2.65	2.72	2.60
Piminodine 5 mg. N = 33 doses	0.80	1.35	1.64	1.50	1.02
Morphine 10 mg. N = 34 doses	0.64	1.12	1.47	1.44	1.40
Piminodine 10 mg. N = 34 doses	0.71	1.59	1.69	1.68	1.55
Morphine 10 mg. N = 41 doses	0.61	1.24	1.46	1.54	1.35
Piminodine 20 mg. N = 40 doses	1.18	1.95	1.46	1.54	1.35

TABLE II. MEAN "INDIVIDUAL" PAIN RELIEF SCORES

DRUG	HOURS AFTER MEDICATION				
	½	1	2	3	4
Morphine 10 mg. N = 13 patients	0.92	2.14	2.67	2.76	2.86
Piminodine 5 mg. N = 17 patients	0.85	1.36	1.75	2.48	2.74
Morphine 10 mg. N = 14 patients	0.57	1.13	1.43	1.49	1.59
Piminodine 10 mg. N = 15 patients	0.74	1.51	1.79	2.05	2.02
Morphine 10 mg. N = 19 patients	0.51	1.39	1.58	1.82	1.69
Piminodine 20 mg. N = 18 patients	1.16	1.68	1.83	1.91	1.96

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TABLE III. MEAN PAIN RELIEF SCORES (FIRST DOSES ONLY)

DRUG	HOURS AFTER MEDICATION				
	½	1	2	3	4
Morphine 10 mg. N = 6	1.0	2.15	2.83	2.15	2.15
Piminodine 5 mg. N = 10	1.0	1.50	1.70	2.0	2.0
Morphine 10 mg. N = 7	0.50	1.43	1.43	1.00	0.67
Piminodine 10 mg. N = 8	0.88	1.62	1.57	1.86	1.50
Morphine 10 mg. N = 8	0.75	1.12	1.38	1.63	1.57
Piminodine 20 mg. N = 10	1.30	1.67	1.88	2.00	1.90

TABLE IV. PER CENT. COMPLETE PAIN RELIEF (ALL DOSES)

DRUG	HOURS AFTER MEDICATION				
	½	1	2	3	4
Morphine 10 mg. N = 34	0	20	52	56	52
Piminodine 5 mg. N = 33	3	8	20	32	34
Morphine 10 mg. N = 34	6	6	14	16	14
Piminodine 10 mg. N = 34	6	12	16	32	34
Morphine 10 mg. N = 41	16	22	23	21	16
Piminodine 20 mg. N = 40	10	30	44	46	24

Incidence of "Successful" Doses (Table V).—An arbitrary definition was established a priori, viz., that to qualify as effective a dose had to supply a pain relief score of at least plus 2 (unless initial pain was described as moderate or slight, when the score had to be plus 1) within the first hour and maintain this degree of relief for at least another hour.

SIDE EFFECTS

The only side effects observed during the study were two episodes of vomiting among the 19 patients who had 20 mg. of piminodine. One patient vomited one hour after the administration of the drug and one 2 hours after piminodine had been given. There was no repetition of the vomiting and both patients later received additional 20 mg. doses of piminodine without any ill effects. Thus from this limited study the incidence of side effects with the new drug appears to be low.

DISCUSSION

Our basic experimental design and method of data collection combine the features of a number of techniques—those of Keele, Houde, and Wallenstein; Denton and Beecher; and Lasagna and Beecher.[4] Although the sets of data presented in Tables I to V answer somewhat different questions, it is reassuring to note that each set leads to similar conclusions, i.e., that 5 mg. of piminodine was less potent than 10 mg. of morphine sulfate, that 10 mg. of piminodine was somewhat more potent than 10 mg. of morphine sulfate, and that 20 mg. of piminodine was clearly more potent than 10 mg. of morphine sulfate.

TABLE V. INCIDENCE OF "SUCCESSFUL" DOSES (ALL DOSES)

DRUG	
Morphine 10 mg. N = 34 doses	70%
Piminodine 5 mg. N = 33 doses	51%
Morphine 10 mg. N = 34 doses	31%
Piminodine 10 mg. N = 34 doses	55%
Morphine 10 mg. N = 41 doses	41%
Piminodine 20 mg. N = 40 doses	75%

The use of all doses employed permits a larger number for statistical analysis, but is at least theoretically susceptible to undue influence by patients requiring a large number of doses. The computation of mean scores for each patient avoids such problems, but does not permit the utilization of the added confidence one ought to have in a mean based on several replicates in one patient as opposed to a "mean" based on only one dose in another patient. The use of first doses only is quite wasteful of data but is an important check on possible drug-order interactions. The "complete pain relief" scores are useful primarily because many clinicians find such data of help in extrapolating to clinical usage. Finally, the incidence of "successful doses" represents an arbitrary criterion employed to allow the use of some single figure to encompass such factors as speed of onset, magnitude of effect, and duration of pain relief.

Sedation was apparently not greater after piminodine than after morphine even when 20 mg. doses of the new drug were employed. A controlled comparison of piminodine and morphine in volunteers, designed specifically to compare the incidence of side actions (including respiratory depression), is obviously needed, and is planned in this laboratory.

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SUMMARY

1. A controlled clinical trial comparing morphine and piminodine (Alvodine) in 96 patients suffering from postoperative pain is reported.

2. When morphine sulfate, 10 mg., was used as the standard for comparison, the equipotent dose of piminodine was found to be approximately 7.5 mg., a figure which is in excellent agreement with the potency of the drug as predicted from the animal data.

3. The side effects observed in this study were minimal with both drugs.

The authors would like to thank the surgical and gynecologic staffs of Baltimore City Hospitals for the opportunity to study their patients and Mrs. Diane Keyes and Mr. Richard Schillaci for collecting the data.

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THE EFFECT OF TRIETHYLENE THIOPHOSPHORAMIDE (THIO-TEPA*) IN THE TREATMENT OF INCURABLE NEOPLASTIC DISEASE

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TRIETHYLENE thiophosphoramide (thio-TEPA), a member of the class of compounds known as ethyleneimines, has been shown to inhibit the growth of certain tumors in mice and rats.[1-7] Reports on the use of thio-TEPA in patients with a variety of malignant diseases have indicated that this drug may be of value in the palliative treatment of advanced cancer.[8-17]

Shay and co-workers obtained the best results with thio-TEPA in chronic myelogenous leukemia, chronic lymphatic leukemia, and carcinoma of the breast, but also obtained some benefit in other malignant tumors.[8-10] Bateman and her associates reported encouraging results in the treatment of advanced carcinoma of the breast and ovary with thio-TEPA.[11-13] Others have also reported variable benefit from the use of thio-TEPA in advanced malignant disease.[14-17] Generally, chronic leukemias, lymphomas, carcinoma of the breast, and carcinoma of the ovary have shown the greatest benefit from thio-TEPA.

The present report deals with our experience with thio-TEPA in the treatment of 60 patients with far-advanced neophastic disease.

MATERIAL AND METHODS

Patients were chosen who had advanced neoplastic disease, proved either at surgery or by biopsy. In many cases, other forms of palliation had already been tried, including surgery, x-ray therapy, and endocrine therapy. The diagnoses, the number of patients in each category, and the results of therapy are listed in Table I.

Thio-TEPA is a white crystalline powder. It was dissolved in sterile isotonic saline to make a final concentration of 10 mg. per milliliter. The solution was sterilized by passage through a Seitz filter and was stored in sterile rubber-capped vials at 5° C. for a maximum of 4 weeks.

*The thio-TEPA employed in this study was furnished through the courtesy of Dr. James Ruegsegger, Lederle Laboratories Division, American Cyanamide Company, Pearl River, N. Y.

TABLE I. PATIENTS TREATED AND RESULTS

DIAGNOSIS	NO. OF PATIENTS TREATED	NO. OF PATIENTS SHOWING IMPROVEMENT*
Carcinoma of breast	13	1
Carcinoma of ovary	10	4
Carcinoma of lung	6	0
Carcinoma of gastrointestinal tract	10	0
Lymphomas	3	0
Carcinoma of cervix	3	1
Carcinoma of kidney	2	0
Melanosarcoma	2	0
Urinary bladder carcinoma	1	1
Bone metastasis (primary unknown)	1	1
Thyroid carcinoma	1	0
Mouth (cheek) carcinoma	1	0
Salivary gland carcinoma	1	0
Carcinoma of pancreas	1	0
Islet cell carcinoma of pancreas	1	0
Carcinoma of lip	1	0
Metastatic carcinoma of liver (primary unknown)	3	0
Total	60	8

*All objective improvement except for bone metastasis (primary unknown).

The thio-TEPA was given intramuscularly except in a few instances when the drug was injected directly into tumor masses. An initial course of therapy consisted of five daily intramuscular injections of 10 mg. each. Two weeks later, if the white blood count remained above 5,000 per cubic millimeter, and if the general condition of the patient had not deteriorated, a second course of five daily intramuscular injections of 10 mg. each was given. Thereafter, 10 mg. was administered intramuscularly at weekly intervals as long as the white blood count remained above 5,000. If the white blood count fell below 5,000, the thio-TEPA was withheld until the white blood count returned to 5,000 or more, at which time the administration of the drug was resumed. The dosage range and number of patients in each group are shown in Table II.

Patients were followed with frequent examinations. Blood counts, consisting of hemoglobin determination, white blood count, differential count, and examination of stained blood films for platelets, were obtained before and after each

TABLE II. TOTAL DOSE OF THIO-TEPA ADMINISTERED

DOSE (MG.)	NO. OF PATIENTS
50	21
50–100	17
100–150	11
150–200	7
Over 200	4
Total	60

course of therapy and preceding each maintenance dose. Platelet counts were performed only when the number of platelets on blood films appeared to be decreased. When x-ray evidence of malignant disease was present, follow-up of the patients included x-ray examinations of the involved areas. A decrease in the size of a palpable mass, improvement in the appearance of a lesion by x-ray, or marked sustained relief of pain in the case of bone lesions was taken as evidence of improvement. Temporary symptomatic improvement such as increase in appetite, decrease in cough, or increased feeling of well-being without other evidence of improvement was not taken as a definite sign of benefit from the drug.

RESULTS

Carcinoma of the Breast.—Thirteen patients with carcinoma of the breast were treated with thio-TEPA. In most of this group many other forms of therapy for metastatic carcinoma of the breast had been used. Only one patient in this group showed objective evidence of improvement following the use of thio-TEPA. This patient was a 50-year-old woman who had had previous treatment with surgery, x-ray, and hormones. Shortly after the first course of thio-TEPA, there was a definite decrease in the size of subcutaneous tumor nodules, marked decrease in pain from bone metastases, and slight improvement in the appearance of the bone metastases by x-ray. The improvement lasted for about one year and a total dose of 520 mg. of thio-TEPA was administered during this time. After one year, there was again progression of the disease in spite of continued therapy with thio-TEPA. Because of marked leukopenia, the drug was discontinued. The patient died one month after therapy was stopped.

Carcinoma of the Ovary.—Ten patients with carcinoma of the ovary were treated with thio-TEPA. Four of the 10 patients showed objective evidence of improvement after therapy with thio-TEPA was started. One patient has had a remission of 34 months and is still receiving 10 mg. of thio-TEPA every 2 weeks. This patient was first seen 5 months following operation and x-ray therapy for carcinoma of the ovary. At that time, a pelvic mass was palpated and ascites was present which on aspiration was positive for malignant cells. At the time of aspiration 20 mg. of nitrogen mustard was injected into the peritoneal cavity and thio-TEPA was started. To date, this patient has received 620 mg. of thio-TEPA. The pelvic mass diminished in size after the first course of 50 mg. of thio-TEPA and gradually disappeared with continued treatment. There has been no recurrence of the pelvic mass or of the ascites. This patient has had mild leukopenia on several occasions but the thio-TEPA has been resumed as soon as the white blood count rose above 5,000 per cubic millimeter.

A second patient was seen 4 years following operation and x-ray therapy for carcinoma of the ovary. At that time, there was a large mass filling the entire pelvis and extending to the umbilicus. There was massive edema of both lower extremities and the patient was taking large amounts of meperidine for relief of pain. Following 100 mg. of thio-TEPA, there was a marked decrease in the size of the mass, the edema of the legs disappeared completely, and the need for

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meperidine was markedly decreased. The remission lasted for approximately 3 months after which the patient's condition rapidly deteriorated in spite of continued thio-TEPA therapy.

The third patient to show objective evidence of benefit from thio-TEPA developed a recurrent pelvic mass and ascites 8 months following removal of an ovarian carcinoma. Shortly thereafter, intestinal obstruction developed. She was treated with intubation and intravenous fluids and thio-TEPA was started. After 50 mg. of thio-TEPA, there was marked decrease in the size of the mass, the obstruction was relieved, and ascites decreased. Thio-TEPA therapy was continued and the remission lasted until 4 months later, when the masses and intestinal obstruction recurred. The patient died shortly thereafter.

The fourth patient was started on thio-TEPA following the incomplete surgical removal of a carcinoma of the ovary with pelvic extension. She died 8 months after the start of therapy, following operation for a ruptured appendix. At the time of operation, no evidence of carcinoma was seen in the abdomen or pelvis. This patient received a total dose of 200 mg. of thio-TEPA.

The remainder of the patients with ovarian carcinoma obtained no objective benefit from thio-TEPA.

Carcinoma of the Uterine Cervix.—Of 3 patients with carcinoma of the cervix treated with thio-TEPA, one showed definite objective evidence of improvement. This patient had a recurrence 3 years following operation and radiation therapy for carcinoma of the cervix. When first seen, she had a large pelvic mass and metastatic nodules in the vagina. Following 100 mg. of thio-TEPA there was marked symptomatic improvement with almost complete relief of pain. There was a definite decrease in the size of the pelvic mass on examination. The patient returned to full-time employment in a plant making electronic parts. The remission lasted approximately 3 months after which invasion of the bladder occurred. In spite of continued therapy with thio-TEPA, she became progressively worse and died several months later.

Other Malignant Tumors.—One patient with a large fungating carcinoma of the urinary bladder, obstruction of one ureter, and a large pelvic mass with a vesicorectal fistula, showed a definite decrease in size of the pelvic mass and decrease in urinary bleeding and closure of the fistula, following the administration of 100 mg. of thio-TEPA. The duration of benefit is not known since the patient was lost to follow-up after discharge from the hospital.

A 70-year-old woman with widespread bone metastases, from a site of unknown origin, was completely bedridden from pain and required constant administration of narcotics for relief. Following the administration of 100 mg. of thio-TEPA, there was complete relief of pain although there were no obvious changes in the appearance of the metastatic lesions by x-ray. The remission lasted for approximately 3 months.

Six patients with carcinoma of the lung, 10 patients with carcinoma of the gastrointestinal tract, 3 patients with malignant lymphomas, 2 with melanosarcomas, 2 with kidney carcinomas, and 9 with a variety of other malignant tumors were also treated with thio-TEPA in doses varying from 50 to 200 mg. None of these patients showed any definite evidence of benefit.

SIDE EFFECTS

The effect of thio-TEPA on the white blood count was extremely variable. Eight patients developed significant leukopenia (white blood count below 4,000 per cubic millimeter) after only 50 mg. of thio-TEPA, while 3 patients received between 150 and 200 mg. of thio-TEPA without any noticeable effect on the white blood count. All patients who received over 200 mg. of thio-TEPA developed significant leukopenia. One patient developed a diffuse purpura after 290 mg. of thio-TEPA with a fall in the platelet count to below 100,000 per cubic millimeter and a marked decrease in platelets on blood films. Thio-TEPA was not resumed in this patient although the platelet count returned to normal after 2 weeks. None of the other patients showed any evidence of hemorrhagic tendency, or of lowering of blood platelets as measured by observation of stained blood films. In most instances, the development of leukopenia was not considered a contraindication to further therapy. Therapy with thio-TEPA was resumed when the white blood count again rose to over 5,000 per cubic millimeter. In 2 patients, however, thio-TEPA was stopped because of severe leukopenia following resumption of therapy. In no instance did permanent agranulocytosis occur.

Nausea and vomiting occurred rarely during the course of therapy with thio-TEPA. In no instance was it a significant problem and never did it require cessation of therapy.

Occasional pain at the site of intramuscular injection occurred. The pain was only momentary and could be completely alleviated by the concomitant injection of 0.5 ml. of 1 per cent procaine.

DISCUSSION

Eight of 60 patients with far-advanced malignant disease showed definite evidence of improvement from the administration of thio-TEPA. The best results were obtained in patients with ovarian carcinoma; 4 of the 10 showed definite objective evidence of improvement. These results are in accord with the reports of other investigators who have also shown worth-while results in ovarian carcinoma.[11,13,14]

In this series, only one of 13 patients with metastatic carcinoma of the breast showed objective evidence of improvement with thio-TEPA. These results are not in agreement with the good effects obtained by Bateman[11,12] in the treatment of breast cancer. Part of the discrepancy may lie in the difference in the route of administration of the thio-TEPA. Bateman,[11,12] used the intratumor route whenever possible and obtained frequent regression of tumor masses. In this series, all the patients received the drug intramuscularly with the object of treating inaccessible metastatic disease rather than localized tumor masses.

Thio-TEPA appears to be of little or no value in the treatment of lung and gastrointestinal cancer. Of 16 patients with gastrointestinal and lung cancer, none responded favorably. On the other hand, one patient with carcinoma of the urinary bladder and one patient with carcinoma of the cervix showed definite temporary benefit from thio-TEPA. No improvement was obtained in 3 patients with malignant lymphoma, 2 patients with melanosarcoma, and in 11 other patients with a variety of other malignant tumors.

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In this series, toxic side effects were not a serious problem. There is disagreement in the literature on the seriousness of the hematopoietic effects of thio-TEPA. Bateman and Carlton[12] reported very little in the way of serious toxicity in the treatment of 122 patients with breast cancer. On the other hand, Ultmann and associates[14] reported serious hematologic toxicity from thio-TEPA. The leukopenic and thrombocytopenic effect of thio-TEPA is unpredictable and in some cases may be delayed for several weeks following a course of therapy. All patients will probably develop some degree of leukopenia or thrombocytopenia if therapy with thio-TEPA is continued indefinitely. Blood counts, including white blood count, differential count, and estimation of platelets by examination of stained blood films, or actual platelet counts, should be taken before and after each course of therapy and before each maintenance dose. Thio-TEPA should not be given when the white blood count falls below 5,000 per cubic millimeter, or when estimation of platelets shows a definite decrease of platelets on stained blood films, or a count below 150,000 per cubic millimeter. The development of leukopenia or thrombocytopenia is not necessarily a contraindication to further therapy. Therapy may be resumed when the blood counts return to normal. However, one must proceed with extreme caution once an episode of leukopenia or thrombocytopenia has occurred. If the white blood count, or platelet count, does not return to normal after 4 weeks, therapy with thio-TEPA should probably be discontinued permanently. By following the precautions outlined above, hematopoietic toxicity was not a factor in the death of any patient in this series.

Continuous maintenance therapy was used in this series whenever possible. If initial improvement was obtained or if the condition of the patient did not significantly deteriorate after the initial two courses of therapy of 50 mg. each, maintenance therapy was instituted. This consisted of the administration of 10 mg. of thio-TEPA at weekly intervals as long as the white blood count and platelet counts remained normal. Therapy was maintained as long as a remission lasted or until it was obvious that the disease was progressing in spite of continued treatment.

With the exception of ovarian carcinoma, the use of thio-TEPA offers only slight hope of palliation in advanced metastatic carcinoma. Even in ovarian carcinoma it should not replace the use of operation and x-ray therapy as a means of palliation. It may be used in conjunction with these modes of treatment or in cases where surgery and x-ray therapy can no longer be used. Although results have been poor in carcinomas other than that of the ovary, an occasional case may respond with a temporary remission. In our hands thio-TEPA has shown no serious toxicity and it is therefore felt that this drug may be tried in any far-advanced malignancy with the hope of obtaining some temporary palliation.

CONCLUSIONS

1. The use of thio-TEPA in 60 patients with far-advanced metastatic carcinoma has been summarized.

2. Eight of the 60 patients have shown objective evidence of remission lasting from several months to over 2 years.

3. The best results were obtained in carcinoma of the ovary. In this group, 4 of 10 patients obtained a remission with thio-TEPA.

4. The development of leukopenia and thrombocytopenia has been the only serious toxic effect of thio-TEPA. In no case was the leukopenia permanent, and in only 2 patients of the entire series was it serious enough to stop further therapy. Only one patient showed a hemorrhagic tendency, associated with a marked decrease in platelets.

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CEREBRAL PALSY: A RE-EVALUATION

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ALMOST 100 years ago, W. J. Little[1] reported on a group of conditions which are now called Little's disease and pointed out the cerebral damage which occurred in babies born after abnormal parturitions, difficult labor, premature birth, and asphyxia neonatorum. Since then, significant strides have been made, particularly in the past decade, in the prevention, diagnosis, and treatment of a group of conditions some of which resemble those cases reported by Little. These conditions are now called cerebral palsy; they result in various degrees of crippling and are responsible for a significant percentage of the total existing chronic disease problems. Progress in this area has been facilitated by the pioneering work of such individuals as Crothers,[2] Phelps,[3] Deaver,[4] and Perlstein[5] and the increasing interest of societies such as the National Society for Crippled Children and Adults and, more recently, the United Cerebral Palsy Association.

In 1947, the American Academy for Cerebral Palsy was formed to coordinate the efforts of physicians in various specialties and to stimulate research in this field. More recently, funds have been made available through the National Institutes of Health, Department of Health, Education, and Welfare, U. S. Public Health Service to support research and to provide training grants in this field.

The development of a statewide cerebral palsy program is typified by the events which have occurred in California. In 1945, following the efforts of interested organizations, the legislature appropriated funds for the establishment of a cerebral palsy program to be used for the following purposes:

1. The establishment of specialized diagnostic centers for children with cerebral palsy.
2. The construction of two residence schools, one in Northern California and one in Southern California.
3. The development of special education and training facilities in public schools for children with cerebral palsy.
4. The provision of medical and surgical care in connection with cerebral palsy.

5. The construction of an institution for children with cerebral palsy who require custodial care.

The State Department of Education had the administrative responsibility for the residence schools and diagnostic centers, with the actual medical supervision carried out under contract with the University of California Medical Center in the northern part of the State and with similar arrangements in Southern California. The State Department of Public Health, through its Crippled Children Services organized in 1927, was given the responsibility for case-finding, preliminary diagnostic examinations at its regular field clinics, and provision of hospitalization for specific medical and surgical care. In addition, this agency was required to cooperate in the development of special classes in the public schools by providing, through local health departments, such physical therapy services as were required for children in attendance. More recently, the State and local health departments have assumed the responsibility for authorization of cases for study in such diagnostic centers as the University of California, while the State Department of Education continues to administer the medical services in the residence schools. The State Department for Mental Hygiene provides institutional facilities for those children who are in need of custodial care.

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Cases for evaluation at the University of California Cerebral Palsy Diagnostic Center are referred by the official agency which administers the Crippled Children's program in a particular community, after screening through a local field clinic of the Crippled Children Services or in the office of a pediatrician. Children are also referred through local Crippled Children Services by private physicians for diagnostic evaluation.

Evaluation in the Cerebral Palsy Diagnostic Center includes such specific studies as are anticipated by information received from the referring agency or physician and from a questionnaire which the family has filled out at the request of the diagnostic center. Every child and his family who report to the diagnostic center are interviewed by a social case worker. Most of the children are examined by a psychologist; all are examined by a pediatrician. Orthopedic and neurological consultation is available, as well as a consultant in speech and hearing to screen those children who might need further evaluation. Any other consultations or tests which are necessary are available at the medical center. After the evaluation of information acquired in this manner, a brief discussion is held by those individuals who have had contact with the family or patient and appropriate recommendations are made. These are usually interpreted to the parents before they leave the clinic by the pediatrician, who acts as coordinator. A summary of the findings and recommendations is sent to the referring agency or physician and includes information regarding admission to the residence or local school, as well as specific advice for therapy and treatment. When the major need is for counseling, appropriate referrals are made to case work agencies.

The State of California, through the Special Education Program of the State Department of Education, in cooperation with the State Department of Public Health and local school and health departments, has provided a network of special day schools for handicapped children—including those with cerebral

palsy. State law permits local schools to allow children from the age of 3 years to 18 years to receive benefits of the special programs. In addition to the educational program, physical therapy, occupational therapy, and speech therapy may also be available, and medical supervision is usually provided by an orthopedist and a pediatrician.

When it becomes apparent that the child cannot benefit from the educational program, he may continue to be seen intermittently by the therapists and physicians in order to prevent any serious deformities and to try to improve the child's physical condition. For many parents it is a great disappointment when the child is no longer permitted to attend the school. They often protest that the lack of educational progress is due to the lack of educational opportunities, without recognizing the child's own limitations. For many parents the school offers custodial care of the child which relieves them of the responsibility for several hours a day. When a child is no longer accepted in school, the parents may find the care difficult and be forced to place the child in a State institution.

What of the child who makes satisfactory adjustment to the special school, who benefits by the educational and therapeutic program available, who finally reaches the school age limit, and for whom the school has no further program? His handicap may still prevent gainful employment. He again becomes a burden on the family, dissatisfied with his lot in life, and discouraged because there are no outlets for him, all of which results in an undesirable situation for everyone.

In some communities there are sheltered workshops for individuals who are no longer eligible for school because of age. These provide a social outlet and are an opportunity for financial gain through development of skills which permit such handicapped individuals to find employment in the community. In some states, organizations, such as the Bureau of Vocational Rehabilitation Services in California, assist in trying to determine aptitudes and skills which can be developed for gainful employment.

Recreational programs for the handicapped have also been developed in some communities which provide a social outlet, an opportunity for the development of hobbies, and pleasure through a program designed for recreational activity. Transportation, however, is one of the major problems in such out-of-the-home activities. In the school program this is solved by budgeting transportation as part of the school cost; however, sheltered workshops and recreation programs are financed through private programs and funds are rarely available for this. Transportation can become a very significant portion of the budget and drain funds excessively.

As the individual with cerebral palsy becomes older, his parents also age and the burden on the family increases—depending upon the degree of the handicap. The parent who could handle the physical needs of the small child is now less able physically to manage the much heavier individual. Where can a family receive assistance for the care of the older physically handicapped individual? Besides the county hospitals for the chronically ill and the State hospitals for the retarded, there are relatively few facilities for physical care over an indefinite period of time.

PROGNOSIS

In the Cerebral Palsy Diagnostic Center certain children were selected for referral to the residence school where, in addition to an educational program, it was possible to carry out prolonged investigation, observation, and therapy in all areas. People trained in various specialties, including physical therapy, occupational therapy, speech therapy, and education—as well as attendants to provide physical care for these children—were available. This presented a unique opportunity for close and constant supervision of children with varying degrees and types of handicaps who had been diagnosed as having cerebral palsy.

It was the hope of the parents and staff that this type of concerted effort by a group of people trained in various specialties would result in dramatic improvement in these children. It became apparent, however, that intensive therapy was not always the answer to their problems. For some, the separation from home was hard and they were unable to remain in the school; in others, motivation was difficult because of a long period of overdependence and lack of response to the treatment available. In spite of an eagerness to improve and a high degree of motivation, some were so physically handicapped that no amount of treatment could accomplish very much. Many, of course, had mild or moderate defects and showed improvement under treatment. Some of the younger children improved in the natural course of development as much as from any specific therapy. Other children were so retarded mentally that they were unable to participate in the therapy sessions in an active way and therefore could not benefit.

The parents, of course, were eager to have their children receive every possible advantage and it was a great disappointment for many of them to realize that even this intensive, almost constant, treatment did not provide the miracle for which they had hoped. It became apparent to them that professional assistance was not the answer to their problem, although they were satisfied that everything was being done for their children.

In considering the prognosis of the cerebral palsy group, it is necessary to consider the associated handicaps:

Convulsions.—There is a high frequency in this group. Published statistics[6-8] indicate that convulsions may occur in 30 to 47 per cent of the cases. In our own clinic, there is a 51 per cent incidence—65 per cent in those suffering from spasticity and 35 per cent in those with athetosis.[9]

Visual Defects.—Reports of visual defects vary from 25 to 50 per cent of all cases of cerebral palsy and include refractive errors and strabismus (especially internal).[6,10,11] In the cases of kernicterus, a characteristic finding is a paralysis in supraversion; other defects include retrolental fibroplasia and nystagmus. Perceptual errors with disturbed perception of form, shape, and depth may also occur. Tizard, Paine, and Crothers[12] found homonymous hemianopsia in 25 per cent of 106 cases of hemiplegia.

Hearing Defects.—These are reported in a greater percentage of children with cerebral palsy than in normal children, particularly in the cases of kernicterus, where the characteristic disturbance is a high frequency loss.[13]

Speech Difficulties.—These have been reported in as many as 70 per cent of cases, with a greater frequency in the athetoid group.[14]

Mental Ability.—The greater the mental ability, the more meaningful will be the education and training of the child with cerebral palsy. While the mental evaluation of the child with cerebral palsy is not simple, a psychologist who has had an opportunity to work with these children can develop a skill at evaluation which can be relatively accurate. A single evaluation cannot always be accepted at face value, but serial evaluations over several years can be very meaningful. If the psychologist's report is not in keeping with the impression of the doctors, therapists, and teachers who are working with the child, it should be approached with some skepticism.

Numerous studies reveal that mental deficiency is present in a much higher percentage of those with cerebral palsy than in the population at large.[15,16] Intelligence quotients below 70 are present in 3 per cent of the population at large, whereas approximately 50 per cent of the children with cerebral palsy have quotients below 70.

Emotional Attitudes.—Even in mildly handicapped and mentally superior individuals, prognosis can be poor if improper emotional attitudes are acquired. Unfortunately, a large proportion of individuals with cerebral palsy do develop poor emotional attitudes. When parents realize that their child is handicapped, they tend to overprotect him; they try to make up to him for his handicap and often make him more dependent than he would be otherwise. They develop guilt feelings, increase their own emotional needs, and make the child more dependent.

One boy who exemplifies this attitude was brought to the Cerebral Palsy Diagnostic Clinic by his mother at the age of 18 years for recommendations in regard to vocational guidance. He had mild athetosis, but could speak intelligibly and had normal intelligence. It was learned that his mother shaved him; he had never been permitted to leave the house alone—his mother had taken him to and from school and she had stayed in the school building to be sure he reached his classes safely.

Parents are not the only offenders in this regard. Well-meaning grandparents, other relatives, and friends add to the child's dependency; also, many normal siblings are required to wait on the handicapped brother or sister.

Another factor in the problem of dependency is the length of time a handicapped child attends a special school. Many are so handicapped that they will never engage in competitive employment and will always require a sheltered or custodial setting. There are some, however, with milder handicaps who can eventually engage in some kind of gainful employment. If these children continue in a dependent, overprotected school environment indefinitely by being transported and waited upon, they will find it difficult to adjust to a world that is not ready to wait on them. An approach to this aspect of the problem is to wean the child away from the special school as early as possible. If the special school is built on the same grounds as that for the physically normal, he can attend regular school classes and return periodically to the special school for therapy and medical observation.

There are few studies regarding emotional attitudes. In a study of 63 individuals over 15 years of age, Wortis and Cooper[17] found that a large number were emotionally disturbed and had many serious social problems. They also found that the family of the child with cerebral palsy was adversely affected by his presence and that the situational difficulty became more destructive to the family as the child grew older, with a complete breakdown of family structure in many families. Where family disorganization existed, the patient with a relatively mild handicap was disturbed in behavior and sometimes became more severely handicapped. In the older patient, the chief problem was lack of social integration. This was also noted in a study by Meyer and Crothers.[2]

Wortis and Cooper[17] noted further that neurotic patterns of behavior and interference with learning activities resulted from overprotective parental behavior. In general, they found that good improvement was not closely related to diagnosis, intelligence, or length of treatment in their clinic. On the other hand, poor improvement was definitely related to the emotional disturbance of the patient as a result of a traumatic family situation or the encouragement of passive, dependent behavior in childhood.

At a Workshop on Rehabilitation held at San Francisco State College in 1957, Dr. William Gellman, Executive Director of the Jewish Vocational Services in Chicago, said that vocational adjustment was most successful with epileptics; next were the mentally retarded, then the emotionally disturbed; least successful were the physically handicapped with associated, marked emotional problems.

In a report by Rennie, Swackhamer, and Woodward[18] 62 per cent of more than 4,000 handicapped individuals were discharged because of social incompetence rather than occupational incompetence.

After reviewing the charts of 72 patients who were enrolled in the Northern California School for Cerebral Palsied Children, we predict that 11 per cent are likely to be independent, 16 per cent might become independent, 48 per cent could function in a sheltered workshop if it is available, and 25 per cent will require custodial care. Some of the 48 per cent who might respond to a sheltered workshop will probably end up in a custodial facility because of the lack of sheltered workshop facilities. Of the total group of 72, 10 per cent had above average intelligence, 40 per cent had average intelligence, and 20 per cent borderline. Mental deficiency, therefore, is not entirely responsible for the poor outlook for this group.

Thirty-seven per cent of the entire group had a mild physical handicap, 40 per cent were moderately handicapped, and 23 per cent were severely handicapped.

Emotional disturbance was evident in many of the case histories, with parents often voluntarily referring to the dependency of their children in such terms as "babying" and "overprotection." The social worker had elicited attitudes which interfered with motivation of the children, and the therapists were also aware of these tendencies. One of the occupational therapists provoked with the lack of effort on the part of a child in learning to dress herself was advised by the child that there was no point in her learning the skill since her mother would do it for her anyway.

Traditional therapy—physical, occupational, or speech—will not alone solve the problems of the child with cerebral palsy and his family. In order to fulfill the potential, it is necessary to determine as soon as possible the facts which relate to the handicap. If parents can be advised early as to the nature and cause of the child's problem, some of the guilt feelings and other attitudes which lead to overdependence of the child might be avoided.

Strengthening of the family is needed to prevent an adverse effect on the emotions of the child; this requires not only good diagnostic evaluation, but good social counseling. The development of more programs for the preschool child in which medical, psychiatric, and social services are available would be helpful. When the child reaches school age, constant review is necessary in order to select children for regular school who need a minimum of therapy. Continued counseling should be available for those families where dependency of the child continues beyond the need. For those children who show some hope of being employable, appropriate counseling should be made available to plan for a reasonable vocation, with eventual referral to the State Vocational Rehabilitation Service.

For many, some form of custodial care or sheltered workshop will be required. Much of what is done in the early years through the efforts of those associated with the special school programs, the Crippled Children Services, and private programs will be wasted unless every effort is made to fulfill the potential of those who might eventually be independent.

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SUMMARY

There has been an increasing interest in the problems of the individual with cerebral palsy. Since 1945 there has been an organized cerebral palsy program in the State of California which has provided for the establishment of specialized diagnostic centers, the construction of residence schools, the development of special education, training facilities in the public schools, and medical-surgical care in connection with cerebral palsy. The program has been a responsibility of the State and local Departments of Education as well as the State and local departments of public health. Special diagnostic facilities have been available at the University of California Medical Center as well as other medical centers.

It has become apparent that individuals with cerebral palsy may have sensory, mental, and emotional problems which may interfere with the prognosis and eventual habilitation of the individual; emotional factors may be the most limiting in relation to the eventual vocational placement and independence. Traditional therapy—physical, occupational, or speech—will not solve the problems of the child with cerebral palsy and his family. Good social counseling is necessary to strengthen the family and to prevent an adverse effect on the emotions of the child. Development of more programs for the preschool child where medical, psychiatric, and social services are available would be helpful. When the child reaches school age, there should be a constant review in order to select those children for regular school who need a minimum of therapy, and continued counseling should be available for those families where the dependency of the child continues beyond the need. For those children who show some hope

of being educable, appropriate counseling should be made available to plan for a reasonable vocation and eventual referral to a state vocational rehabilitation service.

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MAINTENANCE OF AMBULATION IN CHILDHOOD MUSCULAR DYSTROPHY

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PROGRESSIVE muscular dystrophy of the pseudohypertrophic or childhood type has been regarded as a progressive disease leading inevitably to bed or wheel chair confinement in almost all patients. In the past, the usual impression has been that if the disease begins before age 6, the child will be in a wheel chair by his teens.[1] Difficulty in standing and walking quickly leads to bed or wheel chair confinement. Loss of ambulation has usually been accepted as part of the natural course of the disease process by both the family and the physician. The number of dystrophic children confined to wheel chairs or bed comprises a large proportion of reported cases. In a group of dystrophic children studied by Morrow and Cohen,[2] one-half were no longer able to walk and therefore were confined to wheel chairs. The change to chair and bed status may occur very early in the disease course. Paul[3] reports that, of 90 patients with muscular dystrophy, 37 per cent ceased walking or were confined to wheel chairs by the age of 6.

This paper describes the factors involved in maintenance of independent ambulation in muscular dystrophy. There is very little information in the medical literature concerning the factors involved in the transition from an ambulatory to a wheel chair status in this disease. The inference is frequently conveyed that the only element in this transition is simple loss of muscle power. However, the minimal muscle strength required for ambulation in the child with muscular dystrophy has never been reported. It is our belief that the loss of independent ambulation in dystrophy is premature in many instances. An analysis of our patients indicates that there are many complicating elements which accelerate and precipitate the transition from active independent ambulation to passive chair or bed existence.

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METHODS AND PROCEDURES

The usual manual muscle testing technique, described by Daniels, Williams, and Worthingham,[4] was used for testing muscle strength. Percentage grades were used in totaling muscle strength and in preparing the graphs. The percentage scale of muscle testing may not exactly represent percentage of "normal" strength but has frequently been used in the literature for approximating muscle strength. For purposes of graphing, the strongest grade obtained at the time of bracing was used. In most instances, there was no more than one-half grade difference in muscle strength between comparable muscles bilaterally; a few cases demonstrated one grade differences.

The recorded measurements of joint motion indicate the degree of limitation in extension for the elbow, hip, and knee. These were determined as accurately as possible to the nearest 5° by means of a goniometer. Limitation in hamstring "length" was recorded in degrees of limitation in knee extension with the hip flexed at 90°. Limitation of ankle dorsiflexion was measured with the knee as fully extended as possible, in order to include gastrocnemius as well as soleus tightness, a normal degree of dorsiflexion being 80° (or 10° of dorsiflexion beyond 90°). Iliotibial band tightness was measured with the patient prone in terms of limitation of hip adduction to a mid-sagittal plane with the hip abducted and extended as fully as possible and the knee partially flexed. It becomes apparent that if there be any significant hip flexor tightness, whether due to the hip flexors themselves or, less frequently, to a flexor component of the iliotibial band, the more marked abduction component of iliotibial band tightness cannot be measured because of difficulty in positioning the iliotibial band over the greater trochanter.

The contractures about joints of the legs were assigned a rating based on an estimate of the severity. The factor used as a reference point was an estimate of the degree of interference with ambulation. The presence or absence of contracture at the knee joint represents the single most significant finding. The severity was expressed on a rating scale of one to four plus.

DEGREE OF SEVERITY OF JOINT CONTRACTURES

1 Plus—Tightness producing difficulty in obtaining passive motion in any major weight-bearing joint except the knee with not more than 10° limitation of passive dorsiflexion in either ankle.

2 Plus—Knee flexion contracture up to 5° may be present or between 10 and 15° limitation in passive dorsiflexion of either ankle (must have one although both limitations may be present).

3 Plus—Knee flexion contracture up to 10° or 15 to 20° limitation in passive ankle dorsiflexion (must have one although both limitations may be present).

4 Plus—Knee flexion contracture greater than 10° or more than 20° limitation in passive ankle dorsiflexion (must have one although both limitations may be present).

The patients with muscular dystrophy have been classified by a system of grading based on functional capacity. This has been used because it provides a simple and accurate method of assessing over-all muscle performance.[5] It repre-

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sents a modification of a previously published functional classification.[6] It is less precise than the determination of muscle strength but it is very useful and is probably more accurate than rough clinical estimates of muscle function which have been used previously. A limitation of this grading scheme is that it reflects principally the strength of the lower extremity, trunk, and pelvic musculature as manifested by ambulation and elevation activities. However, this relative defect is minimized in muscular dystrophy because muscle degeneration with subsequent weakness in the upper extremities roughly parallels that seen in trunk and lower extremities.[7] Patients are graded on a scale of 1 through 10, with the higher classifications representing progressively severer involvement.

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CRITERIA FOR FUNCTIONAL CLASSIFICATION

1. Obvious defect in posture and walking stance but walks and climbs stairs without assistance.
2. Walks but climbs steps only with aid of railing.
3. Walks but climbs eight standard steps with aid of railing in over 25 seconds.
4. Walks but cannot climb steps.
5. Walks unassisted but cannot climb steps or get out of chair.
6. Walks only with assistance of braces.
7. In wheel chair. Sits erect, can roll chair and perform bed or chair activities of daily living.
8. In wheel chair. Sits erect, unable to perform bed and chair activities without assistance.
9. In wheel chair. Sits erect only with support. Able to do only minimal activities of daily living.
10. In bed, can do no activities of daily living without assistance.

The effect of emotional factors on ambulation has been rated on a one to four plus scale as a result of clinical observations.

EFFECT OF EMOTIONAL FACTORS ON AMBULATION

1 Plus—Slight reduction in ambulation because of emotional factors.

2 Plus—Marked reduction in ambulation secondary to emotional factors.

3 Plus—Transient cessation of ambulation without physical reason. Walking instituted spontaneously

4 Plus—Permanent cessation of ambulation associated with severe emotional trauma.

MEDICAL FINDINGS

The group studied includes 60 patients with progressive muscular dystrophy of the childhood type who have been followed by the authors for periods up to 5 years. Three-quarters of the group are ambulatory at the present time. The ambulatory patients are divided into 2 groups. Fourteen are able to walk only with long leg braces and the remaining 31 walk independently. Fifteen of the patients are unable to walk independently and are confined to wheel chairs or bed. The major focus of this paper will be on 26 patients who no longer walk independently. In 12 of the patients who are in wheel chairs and 14 who walk independently only with long leg braces, there are adequate clinical data for an analysis of the mechanisms which led to loss of independent ambulation.

The total number of patients with childhood type dystrophy in wheel chairs is 15. This represents one-quarter of all patients. All these patients were in wheel

TABLE I. FACTORS IN LOSS OF AMBULATION IN MUSCULAR DYSTROPHY PATIENTS IN WHEEL CHAIRS

CASE	AGE AT FIRST SYMPTOMS (YR.)	AGE AT LOSS OF AMBULATION (YR.)	DURATION OF AMBULATORY STATUS (YR.)	RESTRICTED PHYSICAL ACTIVITY	CONTRACTURES	EMOTIONAL PROBLEMS	MEDICAL ILLNESS	INJURY	OBESITY	PREMATURE LOSS OF AMBULATION
1	5	9	4			+				Yes
2	6	8	2	+	+		+		+	Yes
3	5	7	2	+		+				Yes
4	7	8	1	+						Yes
5	4	8	4	+	+					No
6	3	8	5	+						No
7	2	10	8	+				+		Yes
8	2	8	6	+						Yes
9	4	11	7	+	+			+		Yes
10	3	5	2				+			Yes
11	2	9	7	+	+			+		Yes
12	3	10	7			+				Yes
Mean	3.8	8.2	4.4							

chairs when first seen. The assessment of the factors involved in loss of independent ambulation was necessarily retrospective. Therefore, it was not possible to measure directly the muscle strength or the state of contractures at the time of wheel chair immobilization. The pertinent clinical factors in 12 of these children are summarized in Table I. Symptoms of muscle weakness appeared by age 6 in all but one of these muscular dystrophy patients. The average age at appearance of symptoms was 3.8 years. This age at onset is in agreement with that reported elsewhere in the literature. All of these children had become wheel chair bound by age 11. This occurred in the average patient at about the eighth year of life. These children had been clinically affected by dystrophy for an average of 4 and one-half years at the time they exchanged their troubled ambulatory independence for permanent wheel chair dependency.

The 4 patients who became chair bound in 2 years or less from the first symptoms of muscle weakness are of particular interest (Cases 2, 3, 4, and 10 in Table I). These 4 children had a significantly shorter period of independence than any of the other patients. The loss of ambulation appeared to be premature in all 4. Three of the children were walking with little difficulty when they were placed at prolonged bed rest for a medical illness in the first 2 cases and for diagnostic testing in the third. Only mild symptoms of muscle weakness were present prior to the bed confinement. The relatively minor degree of weakness is well illustrated in the fourth patient who was prematurely wheel chair bound. After a fall, the statement, "I cannot walk," was accepted at face value and he was placed in a wheel chair. At the time he was placed in a wheel chair he was strong enough to get up from the floor unassisted. When muscle weakness is the principal factor in loss of walking, the ability to rise from the floor unassisted has been lost many months earlier. Seven of the remaining 8 patients in this group or a total of 10 out of 12 appear to have gone into the wheel chair prematurely. The incidence of premature chair confinement is much higher than in the group of patients now in long leg braces. This suggests the positive effect of early comprehensive medical management in preventing early chair confinement.

Fourteen patients with muscular dystrophy are ambulatory but require long leg braces for independent ambulation. The braces used have been the double upright long leg type.[8] All but 2 of these patients had been observed at one to 3 month periods for one to 5 years prior to bracing. Symptoms of muscle weakness appeared at approximately the same age as in the wheel chair patients. The first signs were observed between the second and sixth years at an average age of just over 3 (Table II). The period from appearance of muscle weakness until loss of independent ambulation averaged 6½ years as compared to 4 years for the wheel chair group. Children were given long leg braces for ambulation when they could no longer walk independently and standing had been decreased to less than one half hour daily. The more closely supervised patients had an average of 2 years additional independent walking before braces were required. This represents a relative increase of 50 per cent in the span of independent ambulation. All but one are still walking independently in braces so that the total increase in ambulation is considerably greater.

TABLE II. FACTORS IN LOSS OF AMBULATION IN MUSCULAR DYSTROPHY PATIENTS WITH LONG LEG BRACES

CASE	AGE AT FIRST SYMPTOM (YR.)	AGE AT BRACING (YR.)	DURATION OF DISEASE BEFORE BRACING (YR.)	FUNCTIONAL CLASS AT BRACING	*TOTAL MUSCLE MASS AT BRACING	CONTRACTURES	EMOTIONAL ELEMENTS	PHYSICAL ACTIVITY RESTRICTED BY		BRACES PREMATURE
								PATIENT	OTHERS	
1	4	11	7	5	188	3+				No
2	6	13	7	5	326	3+			3+	No
3	4	9	5	5	318	4+	2+	3+		No
4	2	8	6	4	344	4+	2+	3+		Yes
5	2	11	9	5	271	4+	3+	3+		No
6	2	8	6	5	315	2+	2+	4+		Yes
7	3	11	8	3	297	4+			4+	Yes
8	4	10	6	4	335	4+		3+		No
9	3	12	9	4	204	4+	2+		4+	Yes
10	2	9	7	5	298	4+			4+	Yes
11	5	9	4	5	289	4+	3+	3+		No
12	2	8	6	5	324	4+	3+	3+		No
13	4	8	4	5	293	3+	2+		3+	No
14	3	9	6	5	233	4+	3+	3+		No
Mean	3.1	9.7	6.6	4.8	288					

*Normal muscle mass is 700.

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No patient of the brace group lost his independence in less than 4 years after onset of the disease. This is in contrast to the other group where one-half had gone into wheel chairs within 4 years. It would appear that the period of expected independent ambulation in the childhood type dystrophy should not be less than 6 years. Since 5 of the 14 patients had to be braced prematurely, the total possible period of independence in childhood dystrophy should be longer.

MUSCLE STRENGTH

Muscle weakness is the essential factor in loss of ambulation in muscular dystrophy despite the multiple factors which modify the date of transition to wheel chair or long leg brace status. A knowledge of the amount of muscle power required for ambulation is important to the physician, for he must decide whether a child is having serious difficulty in ambulation because of loss of muscle power per se or because of other factors which may, in certain instances, be nonphysical.

Patients who require braces for ambulation had lost more than one-half of their total muscle mass (Table II). The numerical expression of normal total muscle mass gives a grade of 700 by the method used in this paper.[5] The residual muscle mass in the individual patient at the time bracing was necessary varied between 188 and 344, although most determinations fell between 290 and 345. Muscle power by itself was not the sole determinant of ambulation. This is illustrated in the patient with the least muscle mass at time of bracing. With a grade of 188, which represents less than 30 per cent residual muscle mass, this patient was able to ambulate independently. The reason appears to be that he had the fewest complications which accelerate loss of ambulation. This patient (Case 1 in Table II) illustrates the small amount of muscle which is necessary for ambulation if other complication factors such as contractures are minimized.

At the time of bracing, all the major extensor muscles of the trunk, hip girdle, and legs which are important for ambulation had lost more than 50 per cent of their strength (Fig. 1). The flexor muscles tended to be relatively stronger than the extensors. The relative preservation of muscle strength in these flexors may be helpful since they may act in reverse fashion to stabilize extension in the erect position.

The gastrocsoleus and hamstring muscles were the strongest of the lower extremity muscles at the time bracing was indicated. However, there was a concomitant association of severe flexion contractures of the lower extremity. This suggests a relationship between relative preservation of flexor muscle strength and contracture development. The quadriceps muscle is one of the most important muscles in the maintenance of independent ambulation. Only one patient was ambulatory with less than 35 per cent of "normal" quadriceps strength. Loss of knee extensor strength below this level almost always leads to loss of independent ambulation unless external knee support is provided by bracing. The weakest major lower extremity muscles at the time bracing was required were the extensors and lateral stabilizers of the hips. No better than 25 per cent normal strength was elicited in the gluteus maximus in any patient at the time of bracing. The patient can tolerate the lack of ability to extend the hip as long as it is possible to keep the knee in extension.

The actual net loss of muscle strength in the 6 month period immediately prior to bracing was very small. The loss of power in any specific muscle in this interval was usually less than half a grade by manual muscle testing. The seemingly insignificant loss of muscle power in individual areas emphasizes the importance of factors other than specific muscle strength in precipitating the transition from the ambulatory state to wheel chair or brace existence. Very small physical changes are critical when more than one-half the total muscle mass has been lost.

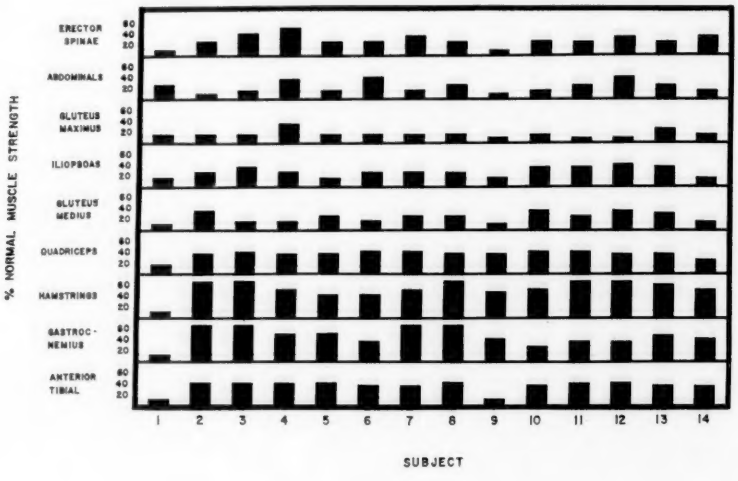

Fig. 1.—Muscle strength at the time of bracing in muscular dystrophy.

EFFECT OF CONTRACTURES

It has long been recognized that patients with advanced muscular dystrophy develop joint contractures.[3] However, the presence and significance of *early* tightness in this disease group has received little mention in the literature. Analysis of patients in University Hospitals Muscular Dystrophy Clinic indicates that tightness and subsequent flexion contractures occur early in the course of the disease.[9] Almost all patients with very early disease, indicated by functional classification in Grade I or II, had already developed tightness and beginning contractures of muscle groups about major joints at the time of their first clinic visit. These include the gastrocsoleus, hamstrings, and iliotibial band. Such tightness in these areas is seen frequently in muscular dystrophy before there is any obvious sign of muscle weakness. As muscle weakness increases, contracture about the joints also becomes more severe and, indeed, often progresses relatively more rapidly than does loss of strength (Table III).

The difficulty in defining the word "contracture" has been pointed out previously.[10-12] The limitation of motion at a particular joint is due initially to muscle and tendon shortening before such a restriction involves the joint structures themselves. The most common limitation in range of motion in muscular

dystrophy patients now in long leg braces was that of dorsiflexion at the ankle. This appeared to be associated with the greater strength of the gastrocsoleus muscle as opposed to the anterior dorsiflexors of the ankle. Limitation was present in 90 per cent of patients at their first clinic visit and in all patients at the time long leg braces were prescribed. The average loss of dorsiflexion at the ankle was 23° with variations between 10 and 50° (Table III). Severe equinovarus foot deformity constituted the end result of gastrocsoleus contracture. It is important to note that the limitation in range of motion at the ankle was present asymmetrically in 11 of 14 patients. Some of the patients had 15 to 30° differences in degree of contracture between the two ankles. Such a difference causes the patient to increase weight bearing on the side with the lesser degree of contracture, quickly leading to progression on the side which is held in the flexed position.

The most serious flexion contracture interfering with independent ambulation is at the knee. It was possible in the closely supervised children to maintain at least 165° of extension at the knee prior to prescription of long leg braces. This is in contrast to the incapacitating knee contractures which developed in the wheel chair patients. Tightness of the hamstring muscles is common in dystrophy and frequently causes collapse of the knees when accompanied by a weak quadriceps.

TABLE III. CONTRACTURES IN 14 PATIENTS WITH MUSCULAR DYSTROPHY AT TIME OF BRACING

CASE	HEEL CORD		KNEE		HAMSTRING		ILIOTIBIAL BAND		HIP	
	R	L	R	L	R	L	R	L	R	L
1	10	10	10	0	0	0	—	—	0	0
2	10	15	5	10	—	—	—	—	—	—
3	25	35	0	0	30	30	35	35	5	5
4	15	30	5	5	10	20	20	20	5	10
5	25	10	15	0	40	25	30	30	5	5
6	15	10	5	0	20	10	40	40	15	5
7	40	40	5	5	35	35	30	30	0	0
8	35	20	5	0	60	50	35	35	15	5
9	40	10	10	0	50	50	—	—	10	0
10	50	40	10	10	55	40	20	25	10	10
11	30	10	10	0	—	—	—	—	0	0
12	15	20	15	15	60	60	—	—	10	10
13	20	20	0	0	10	10	20	15	5	10
14	15	35	0	0	35	45	35	35	10	15
Average	25	22	10	10	30	35	30	30	9	8

At the time bracing was necessary the average tightness in the hamstrings was 32° despite routine prescription of stretching exercises. Iliotibial band tightness is important because of its role in aggravating potential asymmetry and deformity.[10] Almost all patients have shown some limitation in hip adduction caused by tightness of this band. This has varied between 15 and 40°. Hip flexion contractures were noted in 9 patients prior to bracing and ranged between 5 and

15°. In our experience, such limitations were due to contractures of the primary hip flexors more than to the flexor components of tight iliotibial bands. The patients with the greater degree of hip flexion contracture had the greater degree of limitation in all the other areas as well. Significant hip flexion contracture interferes with maintaining the line of gravity posterior to the hip joint, a requirement for balance when standing with the poor hip extensor strength seen in muscular dystrophy.

The multiple flexion contractures of the lower extremity appear to contribute directly to the loss of ambulation. This occurs through a variety of mechanisms. One mechanism is the inability to walk with marked asymmetrical gastrocnemius-soleus contracture because of difficulty in "pushing off." Another factor is the instability of the body in the presence of heel cord contractures, the latter reducing the base for standing by shifting weight bearing to the forefoot. Knee joint contractures tend to increase this instability and result in sudden falls which are extremely frightening to the child. Pain about the joints is a secondary effect of contractures. This has been noted particularly around the outside of the knee joint with tight iliotibial bands. Standing on feet which have marked equinovarus deformity is also painful. Contracture and tightness about any one of the weight-bearing joints lead to further contractures of other weight-bearing joints on the same side. This is due to the position of flexion in one joint frequently being associated with flexion in other joints and indicates the need for a program of stretching to be initiated early for all weight-bearing joints.

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INACTIVITY IN MUSCULAR DYSTROPHY

Physical activity decreases as muscular dystrophy progresses until almost all activity is sedentary. The decrease in activity does not correlate directly with loss of trunk and lower extremity muscle strength because the children anticipate future lower functional status and decrease physical activity prematurely.

The degree of restriction of physical activity in progressive muscular dystrophy has been divided into four grades for purposes of classification.

Activity Restriction in Muscular Dystrophy

Plus 1—Slight decrease in normal ambulatory pattern of activity.

Plus 2—Definite decrease in strenuous physical activities and lessened daily period of ambulation.

Plus 3—Decrease in all types of ambulatory activity. Estimated time walking and standing less than 2 hours per day.

Plus 4—Minimal ambulation or standing time. Less than one-half hour daily spent in walking and standing.

The total decrease in activity is caused by the interaction of multiple factors. The end result is secondary disuse atrophy of muscle. Progressive decrease in activity was noted in all but one of the children going into braces. A similar situation occurred in the wheel chair group. It was estimated that most of the children spent less than 2 hours daily on their feet immediately prior to bracing. Some stood less than 15 minutes in an entire day. Standing for adequate periods daily is important since it not only decreases disuse atrophy but is the best method

for controlling flexion contractures of the weight-bearing joints. Bracing for ambulation should be prescribed when the child spends less than one-half hour standing daily, or the rapid progression of contractures, especially in the knees, may make future bracing impossible. Three hours of standing daily is the minimum requirement for continued independence from braces or wheel chair.

ROLE OF INJURY AND BED REST IN LOSS OF AMBULATION

Acute traumatic injury to an extremity and bed rest during a medical illness played important roles in the loss of ambulation in the present wheel chair group of patients. Four of the 13 patients in wheel chairs ceased walking permanently after a fall. The trauma was minor in 3 of the patients, involving a sprained ankle in 2 cases and a bruised leg in the third. There was a fracture of the ankle in the fourth case. Of the 14 children ambulatory in braces, injury was a factor in causing temporary wheel chair confinement in only one instance. A 9-year-old boy fell while getting off the school bus and sustained a mild sprained ankle. He was put in a wheel chair at school because of slight pain on attempted walking and had not walked for 18 months when first seen in the clinic. These mild injuries had serious consequences since they led to permanent wheel chair confinement in 4 children and 18 months of unnecessary chair confinement in the last boy. Prolonged inactivity sitting in a wheel chair with flexed joints causes disuse atrophy of muscle and favors rapid progression of flexion contractures. There is an inverse ration between the possibility of mobilizing the wheel chair bound dystrophic patient and the duration of chair status. Occasionally, as little as one week of wheel chair confinement may be irreversible. After 2 weeks in a wheel chair, the difficulty in remobilization increases by geometric proportions. Without an active physical therapy program, 3 to 4 weeks of inactivity will generally lead to permanent chair status.

An injury or fracture of a leg should not necessarily cause a dystrophic child to become wheel chair bound if appropriate medical care is initiated promptly. Families are instructed to report immediately any injury which causes pain or inability to walk. A program to preserve muscle power by minimizing disuse atrophy is started immediately. Because the immediate postinjury period is so important, even mild injuries to the legs are usually best treated in a hospital where intensive supervised physical therapy with adequate weight bearing can be initiated early. Weight bearing should be started within a few days in the dystrophic child with an ankle sprain. This usually prevents any permanent loss of muscle power or joint mobility.

Most fractures of the leg, although more serious, can usually be managed so that there is no permanent decrease in fuctional ability. This requires orthopedic measures specifically designed for the dystrophic child. The injured part should be treated when possible without immobilization by a heavy plaster cast. The broken bone can be splinted either in a light walking cast or by use of long leg double upright braces. This is combined with prompt institution of physical therapy. Four ambulatory dystrophic patients have sustained leg fractures without bone displacement. Three had no permanent functional loss due to the

injury. The fourth child, who was ambulatory in braces, fell out of a wheel chair that was being used for temporary transportation at summer camp. The fracture of the femur healed satisfactorily but he did not regain the ability to walk in braces. This failure was due to severe ankle contractures present at the time of injury which prevented adequate standing in a plaster walking cast.

Bed rest for medical illness can also cause loss of independent ambulation. Minor increases in weakness of muscles and tightening of joints are observed after only a few days in bed for an upper respiratory infection. Prolonged bed rest may lead to more serious loss of strength and may even cause permanent confinement to bed and chair. Walton noted that 8 of 24 dystrophic patients confined to bed during the course of exanthemas or other disease had marked exacerbation of muscular weakness.[13] Thirteen showed a mild increase in weakness. The increase in disability was permanent in 7 and 10 patients in these 2 groups cited by Walton. He does not state whether this increase in disability caused loss of independent ambulation. Bed rest in 4 of our wheel chair cases was followed by loss of independent walking. Three of the 4 children never walked again following the period of bed confinement, and the fourth child, although able to walk briefly, soon afterward became permanently wheel chair bound. One boy ceased walking after mild "grippe" of several days' duration. He had fairly severe weakness prior to this illness, and the bed rest merely accelerated the transition to wheel chair confinement. There were 2 instances of completely unnecessary premature loss of ambulation due to prolonged bed rest. A 6-year-old boy was admitted to a hospital for diagnostic tests in the first year of symptomatic muscle weakness. He was kept at bed rest for several months for intensive medical tests and was discharged in a wheel chair unable to walk due to severe knee contractures and muscle weakness. A similar result in another boy followed several months of bed rest following pneumonia.

Forty per cent of the muscular dystrophy cases now in wheel chairs made this transition following an acute injury or medical illness with confinement to bed or chair. Alertness to the unfavorable effects of such inactivity probably would have allowed all these children some months or years of additional independent ambulation. Any illness or injury which requires the dystrophic child to be off his feet for over 3 days requires the mandatory institution of exercises to preserve muscle strength. The program should include standing to preserve equilibratory adjustments and to stretch joint contractures combined with an active exercise program to preserve muscle power and range of motion. Bracing because of increased weakness following illness or injury has been seen rarely in closely followed cases. Under conditions of adequate supervision, there should be little permanent clinical deterioration following injury or medical illness in the child with muscular dystrophy.

ROLE OF OBESITY

It has been previously indicated that weight control is essential to the success of any rehabilitation program in progressive muscular dystrophy.[14] This is particularly true when the child reaches the critical stage where there is just enough muscle strength for precarious walking. A slight increase in weight at

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this time adds greatly to the problem of ambulation. The physician must not incorrectly attribute decreased functional ability to increase in the severity of the muscle disease.

Four of the children now walking with braces had marked increases in weight which interfered seriously with ambulation. The weight gain in these children averaged 15 pounds over a period of 11 months and represented an increase of 20 to 25 per cent in the total body weight. Reduction of weight by diet was successful in 3 of the patients with a decrease in the number of falls daily and an objective functional improvement. Excessive weight gain was an important element in the transition from independence to walking with long leg braces in one of these 4 cases. This child (Case 9 in Table II) gained 22 pounds over an 11 month period with the principal weight gain occurring during the last 2 months of the period. This weight gain was equivalent to almost 30 per cent of his initial weight. Weight gain occurs because the child's food intake is far in excess of his reduced energy demands. In the majority of ambulatory children, it has been possible to control excessive weight gain by meticulous attention to weight and food intake. Attempts at weight reduction have been particularly discouraging in the wheel chair bound children, because of a combination of psychic overeating, pampering, and the minimal energy demands.

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ENVIRONMENTAL FACTORS

Parents, physicans, and school authorities often supplied the impetus for the change to wheel chair status. Since they felt the wheel chair was an unavoidable end result, they often hurried the transition process in the belief that injury could be avoided. The wheel chair was accepted as it was felt to be a more efficient way of handling the children. In 5 of 13 wheel chair patients and 3 in braces, the school authorities were responsible for placing a child in a wheel chair when he was still ambulating independently. This event occurred either following a minor injury, a fall, or for reasons of efficiency in getting from one class to another. The child could have continued walking in most cases with encouragement and a minimum supportive physical therapy program. In several of the cases, the family tried to keep the child ambulatory at home but were unsuccessful because the child spent all day at school immobilized in a wheel chair. Two children had to be given braces because they had been placed in wheel chairs for several weeks at summer camp.

The short term gains in easier handling of the dystrophic child in camp or school by use of the wheel chair must be measured against the long-term sequelae. These include increase in severity of contractures, excessive weight gain with resultant inability to attend school because of problems in transferring on buses, and increased difficulty in handling the child at home. There is also more physical and emotional dependency on the mother. When the child is forced to stop school attendance, social isolation and cessation of any real intellectual growth are added to the physical disability.[15] The end result of premature use of the wheel chair is a lonely, overweight child whose physical, social, and intellectual development has often been arrested at the level attained when the chair was prescribed.

EMOTIONAL FACTORS

The occurrence of serious emotional reactions in the child with muscular dystrophy has been reported in a number of recent papers. Schoelly and Frazer[16] made the observation that the psychological reactions in muscular dystrophy are different from those in other crippling locomotor diseases of childhood (such as cerebral palsy and poliomyelitis), because of its slowly progressive nature, with the patient and family as well as the doctor frequently expecting death around puberty or early adulthood. The same authors noted a withdrawal from the outside world to fantasy life with increased passivity and dependency. Whining, dependency, demandingness, low frustration threshold, lack of ambition and spontaneity, and passive aggressive behavior were very common.[17]

Our experience in childhood dystrophy is in agreement with these findings. The patients react to their illness with a great deal of anxiety. This is often centered on a marked fear of falling and injury.[18] Psychiatric histories of our patients also reveal poor adjustments at home. Furthermore, studies done by the occupational therapist showed these children did much less for themselves than could be accounted for on a physical basis. Milhorat[19] has pointed out the increment of physical disability caused by emotional factors. He used the term *forgotten assets* to indicate that the muscular dystrophy patient may accept a level of performance that is actually lower than his capabilities.

Emotional factors may directly affect independent ambulation. This nonphysical causation of decreased ambulation has been given little attention. Eight of the children in braces showed evidence of emotional factors which interfered with continued walking. Fear of falling was one of the most frequent causes of anxiety. This becomes particularly important after muscle weakness is moderately severe. The anxiety concerning falling is justified, since there is neither the muscle strength nor the proper vertical alignment of joints for postural stability. The fall of the dystrophic child occurs suddenly and without any obvious precipitating cause. The knees buckle without warning and there is a completely uncontrolled crash to the floor. This occurs most frequently during walking, when the weight is transferred to the side with the more severe flexion contractures and walking, as one of the most anxiety provoking situations, is reduced to a minimum. The phase of decreased activity may be succeeded by sudden unexpected cessation of walking not explicable by any change in muscle strength. Following a bad fall there may be a great increase in anxiety and the child may become panic stricken when asked to walk. A period of self-imposed immobilization follows which may last from one or 2 days to a week. If families are properly oriented concerning the handling of these episodes they can reassure and encourage the child so that he spontaneously begins to walk again. Sudden cessation of walking without physical explanation followed by spontaneous reinstitution of independent walking is characteristic of emotionally controlled episodes.

More serious and prolonged periods of self-immobilization follow events with greater emotional significance to the patient. Such events may be a separation from a loved person, birth of a sibling, or hearing a frightening description of the clinical course of muscular dystrophy on radio or television. One-third

of the children now in braces temporarily stopped walking for periods of time up to 2 weeks following such psychic trauma as radio programs where the course of muscular dystrophy was graphically described in the following terms: "First they can no longer walk, then they can no longer feed themselves, and finally they die." During periods of emotionally induced self-immobilization the patients complain that they cannot stand or walk. They may also state that leg pain prevents them from walking. The pain disappears spontaneously with return of independent walking and no satisfactory physical explanation is found for its occurrence.

The most serious physical effect of emotional factors is permanent cessation of walking. This has been seen in 3 cases in which premature confinement was a direct result of emotional factors. The families of these children were prepared psychologically to accept this deterioration as part of the natural course of dystrophy through lack of adequate medical orientation about muscular dystrophy. One case illustrates particularly well the importance of psychic factors in the transition to the wheel chair state.

Case 12.—A 10-year-old Negro boy had muscle weakness since the age of 3. However, he was walking well and still climbing stairs. This amount of activity is an indication that the muscle weakness was relatively moderate. On his tenth birthday he stopped walking suddenly stating that he couldn't walk. The acute loss of ambulation occurred without apparent physical cause. It appeared to be related to the date of death of an older brother with muscular dystrophy who had died from pneumonia on his twelfth birthday.

This boy was not urged to try to continue walking by his parents and no medical advice was obtained at the time of his sudden cessation of walking. He was seen in the clinic for the first time after 6 months of wheel chair existence. Evidence for the prematurity of his transition to this lower physical status was obtained by manual muscle testing. Despite 6 months of inactivity with attendant disuse atrophy, his muscle strength of 340 units compared favorably with that of ambulatory patients. Because of severe knee contractures independent ambulation in braces was never achieved in this boy despite intensive efforts.

The passivity and depression which are characteristic of the muscular dystrophy patient are coupled with a lack of motivation for walking so that patients do not stand or walk enough to maintain maximal physiologic muscle stimulation. They are unresponsive to persuasion or logic concerning their need for greater physical activity. A poverty of expression and affect makes communication difficult. These negative reaction patterns increase with the progression of weakness. The cycle of depression, leading to decreased activity with further disuse of muscle and more depression may continue until the wheel chair ends this phase of the disease. This cycle can be broken by long leg braces, appropriate physical therapy, and occasionally surgery, permitting independent ambulation once again. There is a marked improvement in personality when they begin walking again after operation and bracing. The motivation for physical activities is greatly improved. Many children stand and walk most of their waking hours. They are much more outgoing and talkative and appear more self-confident.

COMMENT

It has been generally accepted that the childhood form of muscular dystrophy progresses inevitably to early wheel chair confinement.[20] Whether such a completely pessimistic appraisal of the disease course and management is justified at present may be questioned. Therapy in the past usually consisted of multiple ineffectual pharmacologic measures without systematic utilization of physical and occupational therapy, orthopedic surgery, and psychiatry.[21] The medical guidance given to the family too often consisted of sympathy and the admonition "to keep the child happy." It has been suggested by some authorities that management should be directed toward preparing the child and his family for wheel chair confinement. This approach stemmed from medical opinion that it was futile to attempt any rehabilitation procedures. This nihilistic approach led to a sense of profound hopelessness and depression on the part of most families and children as well as overprotection and pampering or rejection of the child. These unhealthy attitudes invite early physical, psychological, and intellectual deterioration.

It is the feeling of the Muscle Clinic of University Hospital that, although independent ambulation in this disease is primarily controlled by the progressive loss of muscle strength, the actual duration of independence in the individual patient is influenced by a variety of contributory factors. The second most important of these factors is joint contracture which probably occurs because of the disproportion between flexor and extensor muscle strength. Disuse atrophy as a result of decreased physical activity was the third factor of consequence that accelerated the transition to braces in 13 of the children. Inactivity was usually self-imposed with progression of disease. However, imposed wheel chair immobilization occurred at school or camp. Emotional factors, obesity, and trauma were other contributing causes for the transition from independent ambulation to braces. The various factors interacted to cause a self-perpetuating vicious cycle. Examination of these multiple factors indicates the complexity of the problems involved in keeping a dystrophic child ambulatory. These contributory elements may be instrumental in precipitating the change to chair or long leg brace status from independent walking. The time when a child becomes wheel chair bound can be definitely retarded by proper medical care with attention not only to muscle strength but also to the other complications which have a deleterious influence on ambulation. Since it is not possible, at present, to influence specifically the muscle degeneration and concomitant weakness adequate management of the extramuscular factors involved in loss of ambulation becomes all the more important, for it is frequently possible to modify them favorably. Whether the life expectancy may also be improved awaits the evaluation that can come only after long-term application of a more positive management philosophy.

SUMMARY

1. Loss of independent ambulation in muscular dystrophy occurs prematurely in most patients now in wheel chairs.

2. An ambulatory status may be prolonged for an average of 2 years by initiating an appropriate stretching and exercise program during the first stages of the disease. The longer one waits, the more difficult it is to derive significant benefit from such a program.

3. The importance of total evaluation of the patient with muscular dystrophy as early as possible cannot be overemphasized. During such an evaluation it is essential that an accurate record of muscle tightness or contracture as well as weakness be obtained, so that any change in status can be assayed as objectively as possible.

4. The principal factor in loss of independent ambulation is progressive muscle weakness. In addition there are multiple contributory factors. These include tightness and contractures, disuse atrophy, emotional elements, medical illness, injury, and obesity. Since it is not possible to influence muscle degeneration specifically, the adequate management of the secondary factors becomes increasingly important.

5. These various factors involved in loss of independent ambulation can interact to perpetuate a vicious cycle of progressive deterioration.

6. Tightness of the gastroc-soleus, hamstrings, and iliotibial band can usually be found before any obvious degree of weakness is seen. The joint contractures are usually more severe on one side.

7. Muscular dystrophy patients had lost approximately one-half of their total muscle mass at the time bracing was required for ambulation.

8. Bilateral long leg double bar braces can prolong the ambulatory status of the child with muscular dystrophy.

9. Emotional factors may interfere with the dystrophic child's motivation for walking. Immobilization may be self-imposed and due to psychic causes. The resultant wheel chair status may become permanent if these factors are not recognized.

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Book Reviews

THE YEAR BOOK OF MEDICINE, 1959-1960 Series. Edited by P. B. Beeson, M.D., C. Muschenheim, M.D., W. B. Castle, M.D., T. R. Harrison, M.D., F. J. Ingelfinger, M.D., and P. K. Bondy, M.D. Chicago, 1959, Year Book Publishers, Inc. Pp. 733, indexed. Price $8.00.

The latest *Year Book of Medicine* continues to provide one of the few real bargains in medical books. The past year's significant papers, selected by experts, are presented in abstract form. This year's volume contains even more than the usual number of valuable "asides" from the highly talented group of editors. As always, Ingelfinger's section (on gastroenterology) is the most interesting and contains the largest number of delightfully informative comments. Beeson's section (on infectious diseases) is also readable, again in line with past performance. A pleasant surprise is the material on endocrinology, which for the last few years has been a relatively weak part of the *Year Books*. In the current volume, Bondy seems to have hit his stride. The sections on cardiovascular, pulmonary, and blood diseases are of less interest, at least to this reader, because in them a substantial amount of space is devoted to important, but highly technical, material not of consuming interest to the ordinary internist. Notwithstanding, the book remains perhaps the best and cheapest postgraduate course in internal medicine.

Louis Lasagna

YEAR BOOK OF DRUG THERAPY, 1959-1960 Series. Edited by Harry Beckman, M.D. Chicago, 1959, Year Book Publishers, Inc. Pp. 656, indexed. Price $8.50.

After all the years that Harry Beckman has been editing this particular *Year Book*, it is refreshing to find him seeking new ways to improve it. This latest member in the series contains a list and discussion of the year's "new" drugs. (The fact that most of them should never have been issued and that many are illogical mixtures of old drugs will be depressing but perhaps instructive for the profession. A careful reading of the list will communicate the message all too clearly to the discerning doctor.) Dr. Beckman gives a fairly well-balanced discussion of the serious problem facing the practicing physician as a result of this flood of useless mediocrity each year.

As usual, the *Year Book* contains much that most doctors have either missed or forgotten, and the editor's comments are usually pithy and entertaining. One disturbing feature is the presence of sloppier abstracting than usual: (1) one article talks about "1.28 Gm. digitalis leaf" as a maintenance dose, (2) another uses epinephrine and norepinephrine interchangeably, (3) a third abstract refers to chlorothiazide and "other types of mercurial diuretics," etc.

Also unfortunate is Dr. Beckman's tendency *not* to comment on certain abstracts. For example, the report on the treatment of deafness with vitamins A and E and the claims for tricyclamol plus phenobarbital as superior to either drug alone when none of the active treatments looked better than placebo seem to this reviewer examples of the phony-baloney variety of medical literature that should have evoked Beckman's bellicose blasts.

Finally, what are "lienteric diarrhea" and "encopresis"? If you don't know, skip page 210 of this book, because there's an abstract on the value of a new drug in their treatment, but you aren't told what they are. But then there are 655 other pages, so perhaps you'd better lay out the $8.50 as usual.

Louis Lasagna

ANTIBIOTICS IN MEDICINE. Edited by Lawrence P. Garrod, M.D. British Medical Bulletin, Vol. 16, No. 1, January, 1960. Pp. 88, not indexed. Price, $3.25.

The *British Medical Bulletin* has done it again. This publication has the habit of tackling subjects that would seem destined to evoke hackneyed symposia, yet actually produces, in its pages, extraordinarily stimulating material. The present issue is no exception. In it are some fascinating basic essays on the chemistry and classification of antibiotics, their mode of action, and the mechanisms of drug resistance and some cogently written sections on the clinical use of antibiotics. Even the last contribution—the search for new antibiotics—is of considerable interest, pointing out as it does the inability of usual "screening" techniques to pick up the antifungal activity of griseofulvin. If there are a few essays that are not quite up to snuff, they seem excusable in view of the high level of the issue as a whole (although how Drs. Dunlop, Murdoch, and Garrod let slip in the erroneous statement about the effects of streptomycin and dihydrostreptomycin on the eighth nerve is a mystery). A tremendous bargain.

Louis Lasagna

HENRY E. SIGERIST ON THE HISTORY OF MEDICINE. Edited and with an introduction by Felix Marti-Ibañez, M.D. Foreword by John F. Fulton, M.D. New York, 1960, M.D. Publications, Inc. Pp. 313, indexed. Price $6.75.

This collection of essays is a most happy inspiration. Professor Sigerist was a scholar of great ability and a person of wit and charm. These writings, published in a variety of places over a quarter of a century, are thus rewarding because they provide not only a grand view of medical history but also many insights into Sigerist's personality. One can find here a defence of balneology, a historical examination of cancer, and a tribute to the discoverer of the water closet. Sigerist's delightful sense of humor peeps through recurrently. He demolishes a German historian as one "who smells Pythagoreans everywhere," and scorns an updated version of Hippocrates with its "display of Greek chorus girls, darlings generously exhibiting their buttocks and other charms." A fine essay on truffles contains the following wry passage:

"The production of American truffles, therefore, would have to be developed as a government project, by Washington 'bureaucrats,' under the auspices of the Department of Agriculture. But then—good God—the truffles thus produced would be socialized truffles. One might even call them 'sovietized truffles,' and it is obvious that no self-respecting Republican could eat them.

"I can well imagine what the reaction to such government truffles grown at the expense of the taxpayer would be. The National Manufactures Association and the Chamber of Commerce would issue a violent protest against such unheard-of government interference that was undermining the American way of life. The Council on Foods and Nutrition of the American Medical Association would investigate the matter and would publish a memorandum pointing out that truffles are un-American, a European racket for which there was no need in this country. They would draw attention to the fact that under our American system we had succeeded in raising the biggest and best turkeys in the world, that there was a turkey for everyone who knew how to ask for it, that bread stuffing was much preferable not only because its nutritional value was much greater than that of truffles but because it conformed to American life. Whereupon the House of Delegates would pass a resolution with all votes against those of California—where good food has always been appreciated—condemning the use of truffles. The doctors of Indiana would even go one step further and would organize an association of American physicians and surgeons, the members of which would pledge themselves never to eat any truffles in whatever form they might be served.

"And so I am afraid that we collectivists who simply adore regimentation and therefore like to eat our turkey truffled with sauce Périgueux will have to wait until the war is over and we again can get truffles from France. And this year we shall for once be individualists and shall prepare our Thanksgiving turkey like everybody else, in the good old American way. See Fannie Merritt Farmer, *The Boston Cooking-School Cook Book*, seventh edition, completely revised by Wilma Lord Perkins, with new illustrations, Boston, Little, Brown & Co., 1942: p. 383, 'Roast turkey'; p. 211, 'New England stuffing: 12 slices bread, ½ inch thick. . . .'"

Louis Lasagna

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ANTIBIOTIC THERAPY FOR STAPHYLOCOCCAL DISEASES. Antibiotics Monographs No. 12. Edited by Henry Welch, Ph.D. and Maxwell Finland, M.D. New York, 1959, Medical Encyclopedia, Inc. Pp. 208, indexed. Price $4.50.

The antibiotic therapy of staphylococcal infections can be quite complex at times, due in part to the relatively large number of therapeutic agents which are available for such treatment. Also, several of the more recently developed antibiotics are used almost exclusively as antistaphylococcal agents, and unless one has frequent reason to treat such infections, details concerning these antibiotics may not be familiar. Therefore, the information in this book is very helpful. The authors have presented comprehensive discussions of erythromycin, oleandomycin, novobiocin, vancomycin, ristocetin, and kanamycin. In individual sections for each agent, the history, antimicrobial activity, pharmacological properties, toxicity and side effects, absorption and excretion, and dosage forms are discussed.

There is an introductory chapter which discusses the background of the present day problem of antibiotic resistant so-called "hospital strains" of staphylococci and a few brief comments on antistaphylococcal agents not discussed in the remainder of the book. In general this chapter is quite good, but there are two statements which warrant some comment. On page 10, the final paragraph mentions the efficacy of penicillin in treating penicillin-sensitive staphylococcal infections of the skin and soft tissues and infers that lesions which might need incision and drainage ordinarily, heal without the benefit of this procedure if penicillin therapy is given. This has not been demonstrated by controlled studies, and while the author furnishes a bibliography, there is no specific reference given for this claim. On page 11, while discussing the treatment of staphylococcal bacteremia with penicillin the author states . . . "It is important to use large and adequate dosage because staphylococci have a pronounced tendency to become resistant and this may be accentuated when inadequate dosages are used." In vivo penicillin resistant staphylococci are resistant by virtue of the fact that they produce penicillinase, and while a quantitative increase in penicillinase production has been observed in vitro, the induction of penicillinase production in a previously penicillin-sensitive staphylococcus has not been described. So, available evidence indicates that, if an individual is infected with a penicillin sensitive staphylococcus, treatment with penicillin will not convert this organism to a penicillin resistant one regardless of the dosage given.

The chapters on the various individual antibiotics are very informative and offer the reader a quick source of reliable information on the newer antistaphylococcal agents.

The final chapter, entitled "Recapitulation and Discussion," is an exceptionally valuable 13 pages, and any person who encounters staphylococcal infections could profit from this well-organized and precise outline of the problems involved in the therapy of these infections.

Harvey Minchew

HANDBOOK OF NEUROLOGICAL DIAGNOSTIC METHODS. By Fletcher McDowell, M.D., and Harold G. Wolff, M.D. Baltimore, 1960, The Williams & Wilkins Co. Pp. 201, not indexed. Price $4.50.

This neurological manual is designed primarily for medical students. Its purpose is admirably attained, in that the manner of eliciting a history and performing a neurological examination is presented in a most logical and thorough fashion. In addition, there is a general description of the ancillary techniques employed in neurological diagnosis which also has distinct value. Some comment, however, may be directed to the Table containing data on the cerebrospinal fluid. The term "metastatic glioma" is ambiguous and the quantitative information on cerebrospinal fluid pressure, cell counts, and protein determinations is too categorical. Also the inclusion of the Health Questionnaire in index form and the portion dealing with the bare minimum of knowledge serve no useful purpose. The inclusion, however, of several acute neurological conditions and their management is justified. These objections are minor, and by no means detract from the basic value of the text. In general this manual is highly recommended. The authors are to be congratulated.

Robert D. Teasdall

A GUIDE TO ANTIBIOTIC THERAPY. By Henry Welch, Ph.D. New York, 1959, Medical Encyclopedia, Inc. Pp. 69. Price $3.00.

The title of this book suggests that a physician faced with the problem of choosing an antibiotic for the treatment of an infectious disease might *readily* find helpful information inside. Such, however, is not the case.

The basic fault of the book is the organization of the material. The author presents the general indications, side effects, major dosage forms, average daily dose, and blood and urine concentrations (using these doses) of 31 antibiotics. The susceptibility of some 56 "important pathogenic microorganisms" to these antibiotics is also given. The sensitivity data are presented in tabular form and the other information is given in succinct statements. There is no table of contents nor index, and the material is arranged alphabetically, but according to the generic name of the antibiotics. Thus, if the reader would like to know what antibiotics are effective against a particular infectious agent he must read through all 31 antibiotics. Since the choice of an antibiotic in the treatment of infections should, whenever possible, be based on knowledge of the specific etiological agent involved, such a format is undesirable. In many instances one must begin antibiotic treatment before such specific knowledge is available, but the choice at this time should also be based on a consideration of what infectious organism is most likely involved. Therefore, even in the initial choice of an antibiotic, before cultural results are known, the basic orientation should be towards what *organism* is probably present and the physician would receive more assistance from this book if it were so designed that he might easily refer to the appropriate antibiotic(s) for a specific organism.

Under the heading "general indications" the author lists the clinical and bacteriological indications for each antibiotic. Many of the clinical terms given cannot be accepted as an indication for that particular antibiotic (or for any antibiotic in some cases) without knowledge of an etiological agent. For example, in discussing the general indications for erythromycin, page 26, among others the author lists "pharyngitis, cellulitis, empyema, laryngitis, and bronchitis." For chloramphenicol, page 18, some of the general indications given are "systemic infections, purulent meningitis with or without bacteremia, septicema, pneumonia (bacterial and primary atypical), sinusitis, and rhinitis." Finally, for novobiocin, page 42, in addition to staphylococcal septicemia and enteritis, the general indications given are "pneumonia, cellulitis, carbuncles, skin abscesses, wound infections, paronychia, and varicose ulcers."

Undoubtedly a great deal of work was required to bring together all the sensitivity data presented, and it is valuable to have the data available in one book. If the reader is interested in finding out what organisms are sensitive to a particular antibiotic and what concentrations of this antibiotic can be obtained in the serum and in the urine if one uses the recommended doses, then this book will prove very helpful.

Harvey Minchew

GOUTY ARTHRITIS AND GOUT. By Thomas E. Weiss, M.D., F.A.C.P., and Albert Segaloff, M.D., F.A.C.P. Springfield, Ill., 1959, Charles C Thomas, Publisher. Pp. 221, indexed. Price $7.50.

This monograph brings the reader up to date on the most recent advances in the physiology, pathology, diagnosis, and treatment of this old and interesting disease. The text is well illustrated and written in an easily readable style. The excellent bibliography alone makes the book a valuable addition to the libraries of departments of medicine.

Unfortunately, there are rather frequent typographic and printing errors or omissions which may be confusing to the reader. It would seem as if the book had been rushed off the press too quickly!

Fully one-third of the text is devoted to treatment and the authors emphasize that modern treatment can usually control the disease satisfactorily although the cause is still unknown.

H. F. Klinefelter, Jr.

PSYCHOPHARMACOLOGY FRONTIERS. Edited by Nathan S. Kline, M.D. Boston, 1959, Little, Brown & Co. Pp. 533, unindexed. Price $10.00.

There are not many volumes published that can challenge this one as a clear-cut example of monumental waste of time, effort, and money. The book is a record of the Proceedings of the Psychopharmacology Symposium held at the Second International Congress of Psychiatry, Zurich, Switzerland, Sept. 2-4, 1957. Because of the lapse of time since the Symposium, most of the material is either well known now or has long since been discarded as erroneous or irrelevant.

Can the volume serve as a historical summary? Alas, no. It is repetitious, tedious, full of ex cathedra statements, short on data, and in more than a few instances unbelievably fatuous (and not only in retrospect, one might add).

Then why publish the book? One answer comes to mind: as a souvenir, a memento for those who were their. (Their pictures are included.) The reviewer extends his sympathies to the Albert and Mary Lasker Foundation, and fourteen drug houses, who footed the bill for much of this.

Moral: Most symposia should be published within six months or not at all. Moral: A poor symposium should be buried; to perpetuate it in print is to inflict, on those fortunate enough to have missed it, the same fate that befell the first unlucky audience.

Louis Lasagna, M.D.

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Announcements

THE 10TH ANNUAL INSTRUMENT SYMPOSIUM AND RESEARCH EQUIPMENT EXHIBIT will take place Oct. 4 through 7, 1960, at the National Institutes of Health, Bethesda, Maryland.

Chairman of the Committee on the Symposium on Recent Developments in Research Methods and Instrumentation is Dr. Herman C. Ellinghausen, Agricultural Research Center, U. S. Department of Agriculture, Beltsville, Maryland. Primary topics for discussion on the scientific program include: (1) fluorescence, (2) infra-red, (3) activation analysis, (4) ultracentrifuge, (5) microscopy, and (6) electrodes.

Chairman of the Committee on Manufacturers' Representatives is Mr. Louis Heiss, American Instrument Co., Inc., 8030 Georgia Ave., Silver Spring, Maryland. Examples of the latest types of research equipment will be exhibited by instrument manufacturers. The Exhibit Manager is Mr. James B. Davis, National Institutes of Health, Bethesda 14, Maryland. Telephone: OLiver 6-4000, Extension 2315.

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THE ARTHRITIS AND RHEUMATISM FOUNDATION offers predoctoral, postdoctoral, and senior investigatorship awards in the fundamental sciences related to arthritis for work beginning July 1, 1961. Deadline for applications is Oct. 31, 1960.

These awards are intended as fellowships to advance the training of young men and women of promise for an investigative or teaching career. They are not in the nature of a grant-in-aid in support of a research project.

The program provides for three awards:

1. *Predoctoral fellowships* are limited to students who hold a bachelor's degree. Each applicant studying for an advanced degree must be acceptable to the individual under whom the work will be done. These Fellowships are tenable for 1 year, with prospect of renewal. Stipends range from $2,000 to $3,000 per year, depending upon the family responsibilities of the Fellow.

2. *Postdoctoral fellowships* are limited to applicants with the degree of Doctor of Medicine or Doctor of Philosophy—or their equivalent. These Fellowships are tenable for 1 year, with prospect of renewal. Stipends range from $5,000 to $7,000 per year, depending upon the family responsibilities of the Fellow.

3. *Senior investigator awards* are made to candidates holding or eligible for a "faculty rank" such as instructor or assistant professor (or equivalent) and who are sponsored by their institution. Stipends are from $7,000 to $10,000 per year and are tenable for 5 years.

A sum of $500 will be paid to cover the laboratory expenses of each postdoctoral fellow. An equal sum will be paid to either cover the tuition expenses or laboratory expenses of each predoctoral fellow. In the case of senior investigators, instead of the $500, an additional 10 per cent of the stipend will go to the institution to be applied to annuity programs, laboratory expenses, travel, etc.

For further information and application forms, address the Medical Director, Arthritis and Rheumatism Foundation, 10 Columbus Circle, New York 19, N. Y.